PEDIATRIC ONCOLOGY: A MODEL OF INNOVATION THROUGH COLLABORATION

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ABSTRACT

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Within the last forty years, the childhood cancer five-year survival rate has increased by more than 45%. The field of pediatric oncology has seen a tremendous growth in outcome and much of this success can be attributed to the diverse collaborative model that it is built upon. A multi-institutional research consortium which encompasses the majority of pediatric cancer treatment centers has led to an extraordinarily high participation rate in clinical trials and consequent surge in clinical and scientific knowledge. Child cancer patients are treated by collaborative oncology teams consisting of doctors from many geographical locations and in a variety of specialties. Furthermore, unilateral team-based care with a multi-disciplinary approach to treatment and the inclusion of fields such as physical therapy, nutrition, social work, and psychology has greatly improved outcomes.

This thesis aims to further understand and characterize the field of pediatric oncology as a model of innovation and paradigm for success through collaboration rather than competition. The purpose of this research is also to understand areas for further growth within pediatric oncology and suggest methods to continue the current trajectory of innovation. This thesis will analyze how this collaborative model can be translated to other fields of medicine, including adult oncology, to spur similar growth. Finally, the ethical implications of treating children with cancer will be considered.

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1 Introduction

Cancer has affected the lives of almost everyone, everywhere. The effects it has on the patient, their family, and their everyday lives are tremendous. Pediatric oncology, especially, places an undue burden on families and young children. This paper will begin by providing an overview of the current state and statistics of childhood cancer in the United States. Included in this background will be information on the pediatric oncology consortium and the nature of clinical trials. Following the background will be an overview of the unique aspects of pediatric oncology and a characterization of the different types of collaboration that define this field. Next, this thesis will analyze deficits in this model, identify areas for future growth, and propose solutions to spark innovation and address gaps in treatment. This thesis will then examine how this model of collaboration can be translated to other fields of medicine, such as adult oncology and other rare disease, to improve outcomes and spur growth. The key ethical considerations that must be taken into account in this field will be evaluated in order to ensure that the advances in treatment are ethically sound and put the patient's best interests first. Finally, this thesis will evaluate the limitations of this model and its potential for transforming patient outcomes given the current state of healthcare.

2 Background

Cancer is defined as the "group of diseases characterized by the growth and spread of abnormal cells".[1] It is the second leading cause of death in adults in the United States[2] and although more rare in children, is still the second leading cause of death beyond infancy[3]. Even though only 1% of all cases of diagnosed cancer are in children[4], it is estimated that in 2016, 10,380 children under the age of 15 will be diagnosed with cancer.[5] The amount of progress made in the field, both through scientific discoveries and treatment outcomes, has been nothing short of astounding. In the mid-1970s, the 5-year survival rate after diagnosis was 58%[6] in children but has dramatically risen to greater than 80% today.[7] In contrast, adult 5-year survival is only at about 68%.[8] The survival rate for adolescents between 15 and 19 is similar to that of younger children.[9] There are no fixed criteria to label a disease as rare, but it is generally understood to be a malignant disorder which has an incidence of six or less per 100,000. By this definition, almost all childhood cancers would be classified as rare.[10]

The causes of most childhood cancers are unknown and are therefore highly difficult to prevent. The most common types of childhood cancers are leukemia (acute lymphoid leukemia

[1] *Cancer Facts and Figures.* American Cancer Society, 2015. www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf
[2] *Statistics for Different Kinds of Cancers.* Centers for Disease Control and Prevention, 20 August 2015. www.cdc.gov/cancer/dcpc/data/types.htm
[3] *The primary cause of death in children is accidents*. "Child Health." *CDC.* 22 February 2016. www.cdc.gov/nchs/fastats/child-health.htm
[4] *Cancer in Children*. American Cancer Society, 27 January 2016. www.cancer.org/cancer/cancerinchildren/detailedguide/cancer-in-children-key-statistics
[5] Siegel, Rebecca L., Kimberly D. Miller, and Ahmedin Jemal. "Cancer statistics, 2016." *CA: a cancer journal for clinicians* 66.1 (2016): 7-30.)
[6] Siegel, 29
[7] *Cancer in Children.*
[8] *Cancer*. NIH, 29 March 2013. https://report.nih.gov/nihfactsheets/viewfactsheet.aspx?csid=75
[9] *Cancer in Children and Adolescents.* NIH: National Cancer Insitute, 12 May 2014. www.cancer.gov/types/childhood-cancers/child-adolescent-cancers-fact-sheet
[10] Gatta, Gemma, et al. "Rare cancers are not so rare: the rare cancer burden in Europe." *European journal of cancer* 47.17 (2011): 2493-2511.

accounts for 75% of all childhood leukemias, brain/ONS cancer, lymphoma, sarcoma, neuroblastoma, Wilms tumor, and retinoblastoma. Leukemia, lymphoma, and brain/ONS cancers affect children the greatest and account for 64% of all cancers in children under the age of 15. The most frequently diagnosed cancer also varies by the age of the patient. While brain/ONS cancers are diagnosed in children of all ages, eye and kidney cancers are more common in younger children and lymphomas are more common in older children.[11]

The success of pediatric oncology is largely driven by the large allocation of resources to treating and curing it. There are an estimated 1,365 pediatric oncology specialists currently practicing in the United States.[12] Not only have children's cancer centers been developed[13] but most of these centers are a part of the consortium known as the Children's Oncology Group (COG), a phenomenon which is non-existent in adult oncology. The COG has an international presence and provides unique access to clinical trials and standardized protocols. Over 90% of children diagnosed with cancer are treated at a COG-affiliated center.[14] A large part of the success in treating children comes from the prevalence of participation in research trials – 60% of children are enrolled in a clinical trial[15] in which the control arm represents the best available therapy[16] while less than 3% of adults participate in a trial.[17] Also unique to the pediatric

[11] "An Analysis of the National Cancer Institute's Investment in Pediatric Cancer Research." *National Cancer Institute,* September 2013, https://www.cancer.gov/types/childhood-cancers/research/pediatric-analysis.pdf
[12] "A Career in Pediatric Hematology-Oncology?" *AAP.* 7 March 2016. www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/section-hematology-oncology/Documents/career_brochure.pdf
[13] Siegel
[14] "About Us." *Children's Oncology Group.* 7 March 2016. www.childrensoncologygroup.org/index.php/aboutus
[15] "Pediatric Clinical Trials." *Children's Healthcare of Atlanta.* 2016. http://www.choa.org/childrens-hospital-services/cancer-and-blood-disorders/research/clinical-trials
[16] Smith, Malcolm A., et al. "Declining childhood and adolescent cancer mortality." *Cancer* 120.16 (2014): 2497-2506.
[17] Unger, Joseph M., et al. "Comparison of survival outcomes among cancer patients treated in and out of clinical trials." *Journal of the National Cancer Institute* 106.3 (2014): dju002.

oncology treatment experience is treating more than just the cancer, the treatment teams for most children can also include nutritionists, psychologists, social workers, and other professionals.[18]

The development of a cancer treatment, particularly drug creation and treatment, is a lengthy process which requires intensive testing in humans.[19] Before anti-cancer drugs are released on to the market, they must first be thoroughly tested which usually occurs through the occurrence of Phase I, II, and III clinical trials.[20] The drug undergoes extensive pre-clinical development before Phase I testing has even begun. In any clinical trial, the number of participants must be considered. Too small of a trial may result in unreliable results, while a trial that is too large can waste resources and expose more patients than necessary to a potentially harmful treatment.[21]

About 60% of all biomedical research in the United States is funded by the private biopharmaceutical sector. The NIH supports 25% of research as the second largest funder. This situation is completely reversed in pediatric oncology. Almost all funding comes from the National Cancer Institute (NCI) within the National Institutes of Health (NIH), followed by private foundations and philanthropies, and the pharmaceutical industry contributes a negligible amount.[22]

The purpose of the Phase I trial is to determine the Maximum Tolerated Dose (MTD) of the drug and the trial is performed in advanced cancer patients who may not be able to receive another treatment.[23] In order to find the MTD, the treatment dose is escalated until the Dose

[18] *Cancer in Children.*
[19] Ananthakrishnan, Revathi, and Sandeep Menon. "Design of oncology clinical trials: a review." *Critical reviews in oncology/hematology* 88.1 (2013): 144-153.
[20] Griffiths, Gareth. "Clinical trials in oncology." *Medicine* 44.1 (2016): 56-58.
[21] Smith, Catrin Tudur, Paula R. Williamson, and Michael W. Beresford. "Methodology of clinical trials for rare diseases." *Best practice & research Clinical rheumatology* 28.2 (2014): 247-262.
[22] Adamson, Peter C., et al. "Drug discovery in paediatric oncology: roadblocks to progress." *Nature Reviews Clinical Oncology* 11.12 (2014): 732-739.
[23] Smith, 2014

Limiting Toxicity (DLT) is reached. The pre-clinical phase will already have demonstrated that the drug is not lethal to humans and shows promise of benefit. Phase I trials often consist of patients with advanced cases who may not be able to receive another treatment as a part of their standard care. There are usually six to eight dosing levels with approximately three patients entered at a given time for a certain level.[24] These trials usually only require a small number of patients, often in the dozens.[25] In traditional Phase I studies, there is a very low chance of personal medical benefit and response rates have been estimated to be around only 5%.[26]

Phase II trials require about a hundred patients or less with a specific type of cancer[27] and these trials aim to test the safety and efficacy of a fixed dose of the drug, essentially acting as a screening stage.[28] The goal of Phase II trials is to examine a drug for safety and dosing considerations in a dose-escalation model in order to further understand efficacy during Phase III. Most Phase II trials have historically designed as single-arm studies with no control group but recently there have been an increased number of randomized designs as the number of novel agents have grown. In randomized trials, trial participants are assigned to either the standard or novel treatment. The information gleaned on safety, activity, and feasibility is used to determine whether the trial should progress to the third phase.[29]

Phase III trials, more commonly known as the randomized control trials, are double-blind and undergo rigorous statistical analysis to confirm that the benefit to ratio is high enough for drug approval.[30] Essentially a Phase III trial aims to understand the clinical outcomes of novel

[24] Griffiths, 2016
[25] Unger, 2014
[26] Kodish, Eric. "Pediatric ethics and early-phase childhood cancer research: Conflicted goals and the prospect of benefit." *Accountability in Research: Policies and Quality Assurance* 10.1 (2003): 17-25.
[27] Smith, 2014
[28] Unger, 2014
[29] Griffiths, 2016
[30] Smith, 2014

agent in comparison to the control arm.[31] During these phases, statistical analysis is used to test the null hypothesis, that there is no treatment effect, against the alternative hypothesis, that there is a treatment effect based on a significant sample size.[32] Trials in this stage require at least 100 participants, with numbers ranging from 100 to the thousands.[33] The challenge for Phase III trials in the realm of rare diseases is that the trial design requires a large and sometimes unfeasible number of participants. Additionally, it is much more difficult to establish a standard of care to test the new therapies against because there is such little evidence available for different areas of case management.[34]

[31] Griffiths, 2016
[32] Billingham, Lucinda, Kinga Malottki, and Neil Steven. "Research methods to change clinical practice for patients with rare cancers." *The Lancet Oncology* 17.2 (2016): e70-e80.
[33] "Phases of Clinical Trials." *National Cancer Institute*, 2012, http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials/phases
[34] Billingham, 2016

3 The Unique Model of Pediatric Oncology

Children diagnosed with cancer are often regarded by society and the medical profession as one of the most important classes of medical patients. The progress of research and treatment is arguably the most significant development in the fight against childhood cancer in the last five decades.[35] Unique to the experience of treating childhood cancer is the legacy of collaboration among medical subspecialties, institutions, study groups, and perhaps most significantly, between parents, researchers, and clinicians.[36] Due to the relatively low rate of cancer incidence and the ratio of pediatric oncologists to patients, a cooperative model is inevitable and necessary to create rigorous treatments that can include clinical research trials.[37]

While most rare diseases have had slow growth and low resource allocation, childhood cancer has avoided that and has had accelerating progress. The successes of pediatric oncology have not been linear and it has not been caused by the development of new drugs. Rather, the innovation has occurred through testing existing adult chemotherapeutic agents in children coupled with advances in surgery, radiation, and intensive care.[38]The high level of participation in clinical trials which operate across different treatment centers and the structure of the pediatric oncology drug development industry have led to the creation of physician teams which can cross state and international boundaries. The existence of the COG has made this experience much more effective and the success of the different facets of the pediatric oncology specialty working

[35] Hudson, Melissa M., Michael P. Link, and Joseph V. Simone. "Milestones in the curability of pediatric cancers." *Journal of Clinical Oncology* 32.23 (2014): 2391-2397.
[36]Hudson, Melissa M., William H. Meyer, and Ching-Hon Pui. "Progress born from a legacy of collaboration." *Journal of Clinical Oncology* (2015): JCO-2015.
[37] O'Leary, Maura, et al. "Progress in childhood cancer: 50 years of research collaboration, a report from the Children's Oncology Group." *Seminars in oncology*. Vol. 35. No. 5. WB Saunders, 2008.
[38] Rose, Klaus. "New drugs for rare diseases in children." *Clinical Therapeutics* 39.2 (2017): 246-252.

together harmoniously largely explains the quality of cancer care and innovation that is found today.[39]

The collaborative and cooperative research of pediatric oncology has been instrumental in improving the lives of children diagnosed with cancer and lowering mortality rates by a significant amount. The incorporation of professionals from a wide range of backgrounds and training in different methodologies led to a faster spreading of ideas and greater novel approaches. This type of collaborative work has also facilitated the practices of consolidating data from a wider range of sources and comparing those results in order to improve outcomes. The cooperative groups have determined which are the most successful agents to be considered in RCTs by comparing alternate protocols and thoroughly examining different new therapeutic agents.[40]

3.1 The Children's Oncology Group

The COG was formed in 2000 when the four existing pediatric oncology clinical trials groups merged together.[41] The four merging institutions included the Children's Cancer Group (CCG), Pediatric Oncology Group (POG), Thabdomyosarcoma Study Group (TSG), and the National Wilms' Tumor Study Group (NWTSG).[42]CCG was formed first in the 1950's to separate treatments of type A and type B cancers. POG was born when the pediatric-focused members of the South West Oncology Group decided to separate from the parent organization and it subsequently expanded internationally.[43] TSG and NWTSG grew from coordinated

[39] Harrod, Virginia. "Practicing Pediatric Oncology." Plan II Premedical Society, February 2016, University of Texas at Austin. Guest Lecture.
[40] Unguru, Yoram. "The successful integration of research and care: how pediatric oncology became the subspecialty in which research defines the standard of care." *Pediatric blood & cancer* 56.7 (2011): 1019-1025.
[41] O'Leary, 2008
[42] Benowitz, Steve. "Children's oncology group looks to increase efficiency, numbers in clinical trials." (2000): 1876-1878.
[43] Murphy, Sharon. "On the Merger of the Pediatric Cancer Trials Cooperative Groups, National Cancer Policy Forum." *National Academies*, 2009.

research trials for two rare cancer subtypes. [44]While competition can be an incentive for innovation in certain situations, the four groups were competing for resources and money in an underfunded area to the detriment of patient care.

Despite concerns that a scientific monopoly would be anti-intellectual, the COG has managed to create a huge number of trials and foster innovation,[45] and now has also expanded into an international organization primarily supported by the National Cancer Institute.[46] Most of its member institutions are either pediatric research centers or teaching hospitals.[47] One of COG's largest successes has been enrolling over 90% of its participating patients into a clinical study.[48] Clinical trials have become the standard for care because pediatricians are willing to participate in protocols written by other investigators. Because the model of these trials is such that the best treatment from one becomes the standard regimen for the next trial, discoveries from the trials are quickly integrated into practice.[49] This can be attributed to both patient registries and a partnership between large academic institutions and smaller community centers.[50]

3.2 The Nature of Research in Pediatric Oncology

The striking enrollment of patients into clinical trials has led to pediatric oncology becoming a paradigm for research.[51] The leading centers of study can be found in the large academic institutions but smaller community centers encourage their patients to enroll in a large,

[44] O'Leary, 2008
[45] Benowitz, 2000
[46] Hansmann, Georg. "Interdisciplinary networks for the treatment of childhood pulmonary vascular disease: what pulmonary hypertension doctors can learn from pediatric oncologists." *Pulmonary circulation* 3.4 (2013): 792-801.
[47] "Pediatric Clinical Trials"
[48] "About Us"
[49] Link, Michael P. "Collaborating to conquer cancer: Lessons from our children." *Journal of Clinical Oncology* 31.7 (2013): 825-832.
[50] Smith, 2014
[51] Pizzo, Philip A., and David G. Poplack. *Principles and practice of pediatric oncology*. Lippincott Williams & Wilkins, 2015.

centrally-managed trial. With this setup, each center can have a more reasonable workload and focus their treatment on one particular subspecialty.[52] With this strong infrastructure to support clinical trials, smaller institutions are able to participate in groundbreaking research and disseminate those discoveries in areas which otherwise may not have access to the newest treatments. Because the large institutions serve as reference laboratories, the latest technology and rare expertise has become available to all patients and treatment centers.[53]

Furthermore, due to the limits placed by the small number of pediatric oncology cases every year, sample size constraints mandate the utilization of multicenter and multidisciplinary clinical trials because no single institution has a large enough sample size to perform an accurate randomized control trial (RCT).[54] The COG enrolls patients from multiple hospitals into the same trial in order to have statistically significant results; this method is called collaborative research and is the basis for COG's function.[55] Pediatric drug oncology has historically lagged behind adult drug development because of the unique issues posed by the nature of childhood cancer; the diseases are rare and special trial designs are necessary to adjust for age-related dosage regimens and formulation as well as sampling schedules.[56] Having a majority of the trials occur through the COG allows for the increased flexibility required to accommodate the special needs of treating childhood cancer.

The cooperative approach has many benefits for patient care. Physicians, patients, and parents are reassured that the treatment is the best possible because the protocols are written by acknowledged experts. Collaboration also allowed for access to tumor tissue which was crucial

[52] Adamson, 2014
[53] O'Leary, 2008
[54] "Pediatric Clinical Trials"
[55] "Children's Oncology Group, Who We Are." *Children's Oncology Group,* 2016, https://childrensoncologygroup.org/index.php/childrens-oncology-group
[56] Rioux, Nathalie, and Nigel J. Waters. "Physiologically Based Pharmacokinetic Modeling in Pediatric Oncology Drug Development." *Drug Metabolism and Disposition* 44.7 (2016): 934-943.

in understanding the mechanisms underlying childhood cancer. Information from tumors is key in determining risk stratification and course of treatment.[57]

As more knowledge is gleaned about cancers the diagnoses of subclassifications are becoming more complex and risk-adjusted therapy approaches are becoming more prevalent, sample size issues have grown causing there to be increased international collaboration as well. Because many of these RCTs are run through the COG, the consortium has been able to amalgamate patient data, scientific ideas, and other resources resulting in a faster than normal rate of innovation.[58] The well-defined treatment protocols put forward by the COG have greatly improved the survival of children compared to those who are treated in a center which is not a consortium member.[59] The standardization of care and the participation of almost all childhood cancer treatment centers have caused the COG to become a mechanism for collaboration and innovation almost unparalleled in the medical field.

Furthermore, most pediatric oncologists are involved in clinical care and research because occurrences of childhood cancer are so rare and the results of studies done in adults usually cannot be generalized to children.[60] In order to prevent huge time lags before a drug becomes available for children, a greater percentage of participants need to be recruited for trials pediatric oncologists have to be investigators as well.[61] The integration of research and medical care makes each oncologist a valuable resource of information, especially when there is such a rare occurrence of each type of pediatric cancer.[62] For example, even leukemia, which is the

[57] Link, 2013
[58] Unger, 2014
[59] Bleyer, W. A. "The US pediatric cancer clinical trials programmes: international implications and the way forward." *European Journal of Cancer* 33.9 (1997): 1439-1447.
[60] de Vries, Martine C., et al. "Ethical issues at the interface of clinical care and research practice in pediatric oncology: a narrative review of parents' and physicians' experiences." *BMC medical ethics* 12.1 (2011): 18.
[61] Hudson, 2014
[62] Hudson, 2015

most common type of childhood cancer, only accounts for 30% of occurrences. The second most common are brain and nervous system cancers (26%) followed by soft tissue sarcomas (7%).[63]

3.3 Multidisciplinary Treatment

Pediatric oncology pioneered the multidisciplinary approach of treatment.[64] The long-established pediatric oncology model dates back to the 1950s and consists of a multidisciplinary approach for diagnosis, treatment, and long-term follow-up.[65] Investigators from different specialties joining together to expedite breakthroughs and build on early success has long been the norm.[66] This methodology of treatment has been advanced even further through the guidelines established by the American Academy of Pediatrics for pediatric cancer centers, which stipulate that each center must have a functional multidisciplinary team dedicated to providing optimal care.[67]

Each treatment team includes a variety of specialists. For example, the multidisciplinary team of the pediatric oncology department at Massachusetts General Hospital includes child psychiatrists, social workers, child life specialists, nutritionists, physical therapists, and rehabilitation medicine specialists.[68] This interdisciplinary approach has been integral in treatment and supportive care and has led to significant improvements in survival and quality of life.[69] One of the most integral members of the team is the mental health professional who interacts with the lead oncologist on at least a daily basis and the quality of psychosocial care of

[63] Siegel, 2016
[64] "Cancer in Children and Adolescents"
[65] Pritchard-Jones, Kathy, et al. "Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries." *The lancet oncology* 14.3 (2013): e95-e103.
[66] Rioux, 2016
[67] Cantrell, Mary Ann, and Kathy Ruble. "Multidisciplinary care in pediatric oncology." *Journal of Multidisciplinary healthcare* 4.1 (2011): 171-181.
[68] "Division of Pediatric Hematology and Oncology." *MassGeneral Hospital for Children,* 2016, http://www.massgeneral.org/children/services/treatmentprograms.aspx?id=1610
[69] Rioux, 2016

children affected with cancer is far superior to that of adults.[70] While psychologists are a component of many teams, it is usually the social worker that serves as the coordinator for psychosocial care, especially in COG-funded institutions.

3.4 Multi-physician Teams

Collaboration among pediatric oncologists is necessary for a variety of reasons and cooperation to this extent is not seen in adult oncology. The relatively low number of cases and high importance of these patients have led to a team-based approach to treatment. If each patient only had one oncologist there would not be enough cases for each physician and quality of care would decrease. Because children with cancer are one of the highest priority patients, hospitals, families, and the healthcare system are willing to allocate generous resources to their treatment, specifically in the form of multiple doctors consulting for one patient.[71] Additionally, as diagnoses and treatments are becoming more complex specialists in different fields are needed. For example, a child with a liver tumor may require a radiation oncologist, oncological surgeon, and hepatologist in addition to their oncologist. Each physician must be involved at every step of the treatment plan in order to increase benefits and mitigate any risks.[72] Experts of rare cancers oftentimes perform on-treatment review, allowing oncologists with limited experience access to knowledge they otherwise would not have.[73] While this type of cooperation exists in adult oncology, it does not match the level and success of that seen in children's cancer care.

Collaboration between physicians is also the result of the way in which the drug industry and research trials operate. Rather than improving the efficiency of a drug, pharmaceutical companies and drug developers create a new drug which has the same end result but with a

[70] Wiener, Lori, et al. "Pediatric psycho-oncology care: standards, guidelines, and consensus reports." *Psycho-Oncology* 24.2 (2015): 204-211.
[71] Ananthakrishnan, 2013
[72] Cantrell, 2011
[73] Murphy, 2009

higher percentage of success and different biological method.[74] Additionally, oncology drugs have some of the highest rates of attrition because of unexpected toxicity or inefficiency.[75] Because of this, new oncology drugs are constantly being released and input from different oncologists is necessary because it is close to impossible for one physician to know every drug available and its effects on a child.[76]

Collaboration among pediatric oncologists has also been naturally heralded through systems of drug labelling. Modern drug labels require proof of efficacy, including dosage information for children, through clinical and regulatory trials. While labelling improved in the 1960's and 1970's, the successes of pediatric oncology did not arise from better product labelling. Children with cancer are treated by highly specialized oncologists who rely on off-label treatments based on nonregulatory clinical trials. As modern labels have increasingly replaced eminence-based decision making, the studies need collaboration by multiple physicians to implement the trial, learn from them, and properly disseminate the new information.[77]

3.5 Major Success Stories: Acute Lymphoblastic Leukemia (ALL) & Ewing's Sarcoma

Extraordinary progress has been made in acute lymphoblastic leukemia (ALL) in recent years through national and international collaborative research resulting in cure rates of 80% in most industrialized countries.[78] The bone marrow overproduces immature lymphocytes, a type of white blood cells, in ALL and red blood cells, white blood cells, and platelets can be affected.[79] About 3,000 individuals under age 20 are found to have ALL each year in the US and current

[74] Ananthakrishnan, 2013
[75] van Hasselt, JG Coen, and Piet H. van der Graaf. "Towards integrative systems pharmacology models in oncology drug development." *Drug Discovery Today: Technologies* 15 (2015): 1-8.
[76] Smith, 2014
[77] Rose, 2017
[78] Pui, Ching-Hon, and Raul C. Ribeiro. "International collaboration on childhood leukemia." *International journal of hematology* 78.5 (2003): 383-389.
[79] "Childhood Acute Lymphoblastic Leukemia." *National Cancer Institute,* 5 February, 2016, https://seer.cancer.gov/statfacts/html/alyl.html

treatments involve a mix of chemotherapy, stem cell transplant, radiation, and targeted therapy.[80] Collaboration has been integral in developing optimal therapy and supportive care for the different types of ALL. A standard therapeutic approach for rare subtypes, such as myeloid leukemia in patients with Down syndrome, has been developed through the partnership of various cooperative research groups.[81] These developments were largely supplemented by international collaborations, including an agreement to combine data from studies between the Associazone Italiana di Ematologia ed Oncologia Pediatrica, Berlin-Frankfurt-Munster Study Group, the Children's Cancer Group, and St. Jude's Children Research Hospital.[82]

Treatment of Ewing's sarcoma (ES), a tumor of bone and soft tissue, has made remarkable progress due to multidisciplinary and international collaborations. The sarcoma usually arises in the bones of the arms, legs, pelvis or chest. Chemotherapy is usually performed first to shrink the size of the tumor followed by surgical removal.[83] About 200 children are diagnosed with Ewig's sarcoma every year in America and about 70% of children with it are cured.[84] However, if the disease is diagnosed after it has spread the survival rate is only 30%.[85] Progress in surgical options and aggressive radiation therapies have both led to large improvements in outcomes. Collaboration between physicians, pathologists, and biologists at an international and national level has led to a virtual and centralized biobanking system with

[80] "Acute Lymphoblastic Leukemia (ALL)." *St. Jude's Children Research Hospital,* 2016, https://www.stjude.org/disease/acute-lymphoblastic-leukemia-all.html
[81] Pui, Ching-Hon, et al. "Childhood acute lymphoblastic leukemia: progress through collaboration." *Journal of Clinical Oncology* 33.27 (2015): 2938-2948.
[82] Cantrell, 2011
[83] "Ewing's Sarcoma." *John Hopkins Medicine,* n.d., http://www.hopkinsmedicine.org/kimmel_cancer_center/centers/pediatric_oncology/cancer_types/ewings_sarcoma.html
[84] "Ewing Sarcoma." *St. Jude Children's Research Hospital*, 2016, https://www.stjude.org/disease/ewing-sarcoma.html
[85] Cantrell, 2011

pretreatment diagnostic ES samples. Cooperative trials in America and Europe have also led to advances in finding a cure and optimizing multimodal therapeutic strategies.

4 Areas for Further Growth

Despite the dramatic rise in survival rates there are still many areas in which pediatric oncology can improve to yield further growth. The field continues to face many challenges to achieving high survival rates for all types of cancer and this section will focus on what areas hold the most promise for growth and what opportunities there are for improvement. Advances in treatment, particularly in the rise of biomarkers and personalized genomics, present unique avenues that can be capitalized upon for better therapeutic agents. Despite historical growth, the current state of child cancer research and treatment will be discussed and the claims of a plateau in innovation addressed. Because drug development continues to be a challenge in treating pediatric cancer patients, the nature of the pharmaceutical industry within pediatric oncology will be explored and recommendations will be given for overcoming barriers within pharma. Policy responses to drug development will also be considered. Finally, specific recommendations to spur further innovation will be presented.

4.1 The Use of Genomics in Cancer Treatment

Cancer genomes amass somatic mutations, including single nucleotide substitutions, insertions or deletions, copy number changes, and chromosomal rearrangements.[86] As a result of massive parallel genomic micro- and nanoarrays, complete genome sequencing is becoming more available at a lower cost. Personal genome sequencing (PGS) can provide a better understanding of the molecular processes involved cancer metastasis and development as well as improve tumor diagnosis.[87] Cancer mutations are diverse in type, number, and functional effects but the genetic markers which PGS tracks can create a mutation profile which indicates

[86] Hudson, Thomas J., et al. "International network of cancer genome projects." *Nature* 464.7291 (2010): 993-998.
[87] Drmanac, Radoje. "The advent of personal genome sequencing." *Genetics in Medicine* 13.3 (2011): 188-190.

susceptibility to disease and likely responses to certain drugs.[88] PGS allows for more optimal treatments, including repurposing drugs for new purposes and diseases.[89] Collaboration has been the driving force in The Cancer Genome Atlas (TCGA), an American endeavor to profile the genomic changes in major types and subtypes of cancer. TCGA has been a collaboration between the National Cancer Institute and National Human Genome Research Institute. It has operated as a national network of research and technology teams which has pooled their results and made their data available for free internationally. This coordinated effort has allowed for the characterization of 33 cancers from tissues of over 11,000 patients.[90] The collaborative model has expanded to an international effort through the creation of the International Cancer Genome Consortium, a merging of the efforts between Canada and the United States.[91]

PCG is not completely reliable and there are still many concerns over the validity and clinical utility of these tests.[92] One way to make this method more applicable and ease concerns is by creating a multidisciplinary research agenda composed of epidemiology, clinical biology, behavioral science, and public health. Clinical studies are necessary to test the effectiveness of PCG data and health services research to ensure the integration of this data into clinical practice is being done in a beneficial way. Epidemiologic studies are necessary for risk characterization and public health research can test if these endeavors are cost-effective and reduce health disparities.[93] Clinical applications will also be improved if the knowledge of oncologists,

[88] Dancey, Janet E., et al. "The genetic basis for cancer treatment decisions." *Cell* 148.3 (2012): 409-420.
[89] Rioux, 2016
[90] "Program Overview." *The Cancer Genome Atlas*, 2016, http://cancergenome.nih.gov/abouttcga/overview
[91] "Children's Oncology Group"
[92] Khoury, Muin J., et al. "The scientific foundation for personal genomics: recommendations from a National Institutes of Health–Centers for Disease Control and Prevention multidisciplinary workshop." *Genetics in Medicine* 11.8 (2009): 559-567.
[93] Pritchard-Jones, 2013

pathologists, biostatisticians, geneticists, policy-makers, and pharmacists is combined in a coordinated effort.[94]

4.2 Pharmaceutical Considerations: Problems in Drug Development and Recommendations

Children with cancer face a major lack of access to new drugs.[95] High income countries, such as the United States, have almost reached an optimization of current anticancer treatments and the growth in rate of survival has greatly slowed since the early 2000s.[96] Scientific progress in treating pediatric oncology has also slowed down because the small market of pediatric oncology fails to provide enough incentive for pharmaceutical companies to vigilantly pursue treatments and cures.[97] The majority of oncology drugs are first developed for adults and then used to treat children after enough years have passed to fully understand its effects. In the past 20 years, only one drug has been developed for pediatric cancer indications.[98] Currently, the industry begins to consider developing a drug for the pediatric cancer patients only after it has reached phase II trials in adults. If there is not sufficient preclinical data to inform this drug development then the process lags even further.[99]

Registering a new therapy for pediatric patients of rare diseases adds another level of complexity to the already difficult drug development process. Disease-specific strategies are needed to engage with parents, caregivers, and a variety of advocates are needed in order to identify and engage pediatric patients. Qualitative measures of treatment evaluation are also difficult to develop because a child may not be able to read a questionnaire, understand the

[94] Gustafson, 2011
[95] Moreno, Lucas, and Andrew DJ Pearson. "Children's clinical cancer trials: what needs to change to allow children access to new cancer drugs?." (2015): 665-667.
[96] Khoury, 2009
[97] Adamson, 2014
[98] Connor, Edward, and Pablo Cure. "'Creating hope" and other incentives for drug development for children." *Science translational medicine* 3.66 (2011): 66cm1-66cm1.
[99] Adamson, 2014

concepts being asked of them, or provide a reliable answer to those questions. Clinical outcome assessments are usually completed by a parent or a caregiver because they have been present as the disease and treatment have progressed over time.[100] As a result, the FDA has recommended that observable measures should be evaluated when gathering informant-reported measures.[101]

While conventional drug development operates in a fairly linear pattern, the opposite is true for rare diseases. Different groups of people oversee each step of a conventional drug development. The leadership of research and development, such as a chief scientific officer of a pharmaceutical company, will interact with academia and discovery laboratories when they identify a drug of interest. Once a lead has been identified, the clinical development team of a pharmaceutical company will work with investigators and regulators to begin trials. After the drug has gone through regulatory approval, commercial and medical affairs work with leaders in the medical community and patients to deliver the treatment. While there is some overlap, each group is usually made of different individuals. In rare diseases, however, there is a large amount of overlap. Investigators are often members of the medical community, patient advocacy organizations have close ties with investigators, and there is greater collaboration between researchers, healthcare providers, and regulatory agencies. Therefore, research and development priorities need to be agreed upon early to ensure a smooth process, especially when there are a limited number of patients.[102]

Research consortia can also be used to improve relations with and serve as a bridge between pharmaceutical companies, patient advocacy groups, primary care doctors, and other

[100] Deal, Linda S., et al. "Patient Voice in Rare Disease Drug Development and Endpoints." *Therapeutic Innovation & Regulatory Science* (2016): 2168479016671559.
[101] US Department of Health and Human Services. "FDA guidance for industry, patient reported outcome measures: use in medical product development to support labeling claims." *FDA, Washington DC*, 2006.
[102] Rudek, Michelle A., and J. M. Korth-Bradley. "Don't Do Different Things… Do Things Differently! Drug Development in Rare Diseases." *Clinical Pharmacology & Therapeutics* 100.4 (2016): 333-335.

health professionals. It has been widely regarded that pharmaceutical companies are generally unwilling to perform trials of new drugs for rare cancers because of limited financial return. However, this trend has begun to reverse in recent years and the question now is how to further incentivize drug companies to pursue these avenues. The reversal has occurred for a number of reasons. One, niche indications sometimes cause faster drug registration with regulatory agencies because there are no other treatments with significant levels of efficacy. Second, if a rare tumor has a well understood driver mutation then the efficacy of a drug can be validated without an RCT because it causes greater tumor response and progression-free survival in patients. Finally, health agencies, patient advocacy groups, and other entities have provided support to create drugs for rare diseases.[103]

Molecularly targeted therapy holds great promise for treating childhood cancer, especially rarer subtypes. However utilization of these strategies faces unique problems in pediatric oncology. Implementation requires an extensive knowledge of the molecular targets and signaling pathways, but this underlying biology differs vastly between adults and children making it difficult to translate high-priority targets in adults to children. Additionally, many pediatric cancers are more genetically complex than adult malignancies, and this heterogeneity makes the cancer more difficult to treat with single agents.[104]

As the saying goes, children are not small adults. Drug dosages are developed in a way that they can be applied to the entire adult population, which poses a serious barrier to their use in children. Physical and developmental changes during childhood affect drug absorption, drug distribution in tissues, and metabolic enzyme expression. The National Cancer Institute (NCI)

[103] Blay, Jean-Yves, et al. "The value of research collaborations and consortia in rare cancers." *The Lancet Oncology* 17.2 (2016): e62-e69.
[104] Norris, Robin E., and Peter C. Adamson. "Challenges and opportunities in childhood cancer drug development." *Nature Reviews Cancer* 12.11 (2012): 776-782.

began the Pediatric Preclinical Testing Program (PPTP) in 2004 as a multi-institutional program for testing new agents in development for the applicability to childhood solid tumors and leukemia using *in vivo* xenograft studies.[105] This program performs testing on pediatric tumors to decide which agents should be prioritized in trials.[106]

As the knowledge of the molecular basis of cancer increases, types of cancers are growingly clustered into sub-species based on their genomic biomarkers. This poses an important problem for pediatric oncology as many childhood cancers are already rare and a biomarker does not always have a corresponding drug in existence. The extremely high costs for research and development of drugs for specific biomarkers and rare diseases are very prohibitive which makes it highly unlikely that private corporations will pursue research in these subtypes. Therefore, more public-private partnerships will be essential in ensuring that R&D for rare subtype treatment is actually pursued.[107]

Biopharmaceutical companies and public research groups will also have to look towards an international collaboration approach to be able to recruit enough participants for their trials. Global coordination will be most necessary in phase 2 trials, which mostly use randomized methods, and phase 3 trials in patients with selected biomarkers.[108] In order for international trials to become more common, definitions of response need to be synchronized between partnering entities, particularly between North America and Europe.[109]

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[105] Connor, 2011

[106] Patlak, Margie, Erin Balogh, and Sharyl J. Nass. *Facilitating Collaborations to Develop Combination Investigational Cancer Therapies: Workshop Summary*. National Academies Press, 2012.

[107] Vassal, Gilles, et al. "New drugs for children and adolescents with cancer: the need for novel development pathways." *The Lancet Oncology* 14.3 (2013): e117-e124.

[108] Cantrell, 2011

[109] Sullivan, Richard, et al. "New policies to address the global burden of childhood cancers." *The Lancet Oncology* 14.3 (2013): e125-e135.

4.3 Policies to Incentivize Drug Development

Within the last twenty years, many important policies and regulatory changes have incentivized pediatric drug development, including The Best Pharmaceutical for Children Act of 1997, the Pediatric Research Equity Act of 1997, and the Creating Hope Act of 2010.[110] The goal of the first two acts was to incentivize the pharmaceutical industry to increase their knowledge of the impact of their drugs on pediatric patients. These two acts have significantly increased the number of drugs with pediatric labeling and have led to the novel use of more than 400 drugs in children.[111] The acts also increased communication between the biopharmaceutical and pediatric oncology clinical research industries.[112] Pediatric development plans are required to be considered at the end of Phase 2 trials, which hypothetically should lead to earlier creation of pediatric evaluation requests in the drug-development timeline.[113] However, many companies received waivers from having to test drug effectiveness in children because cancer drugs are labeled based on pathological traits which allowed relevant but pathologically distant pediatric cancers to be avoided.[114]

While many of the unique aspects of pediatric oncology can be applied to the adult field, it is also important to increase collaboration between researchers in adult and pediatric oncology. Due to the nature of pediatric cancer drug development, the adult oncology drug field must be able to efficiently and effectively share their knowledge and data with pediatric researchers. It is, however, important to note that while it may take time for breakthroughs in adult cancer

[110] Rioux, 2016
[111] Christensen, Michael L. "Best pharmaceuticals for children act and pediatric research equity act: time for permanent status." *The journal of pediatric pharmacology and therapeutics: JPPT: the official journal of PPAG* 17.2 (2012): 140-141.)
[112] Blay, 2016
[113] Smith, 2014
[114] Blay, 2016

treatments to reach pediatrics, improved treatment regimens diffuse quickly for childhood cancers due to the high participation of patients in clinical trials.[115]

The Creating Hope Act of 2010 is a priority review voucher[116] with the FDA[117] meant to incentivize the development of new drugs exclusively for rare pediatric diseases. Successful drug development for rare diseases such as pediatric oncology requires collaboration between the government and industry. The government can enable early studies to reduce the risk of candidate drugs, but the pharmaceutical industry is needed for later clinical development and to actually produce the products.[118] The transformation of adult drugs into pediatric drugs by pharmaceutical companies, however, can come at a cost. The companies developing adult drugs must meet regulatory requirements for those products which take the focus away from groups solely focusing on pediatric oncology. This causes the highly integrated and collaborative pediatric oncology community to become fragmented and jeopardizes the unified clinical activities which are needed for the small number of child cancer patients.[119]

4.4 Recommendations for Further Innovation and Collaboration

The recent plateau in mortality rates and remaining cancers with very poor treatment outcomes clearly demonstrate that there is a strong need for the development of novel therapies and modifying the use of currently available chemotherapeutics is not sufficient.[120]The cell signaling pathways in cancer cells have undergone multiple mutations and treating only one pathway oftentimes leads to relapse or resistance. Therefore, combination therapies which target multiple pathways are key to improving response and studies have shown that treatment with two

[115] Christensen, 2012
[116] Connor, 2011
[117] Smith, 2014
[118] Connor, 2011
[119] Christensen, 2012
[120] Kearns, Pamela, and Bruce Morland. "New drug development in childhood cancer." *Current opinion in pediatrics* 26.1 (2014): 37-42.

drugs simultaneously is much more effective than sequential treatment.[121] This type of therapy, however, commonly requires drugs with intellectual property rights held by different companies and collaboration among companies, organizations, and institutions is oftentimes difficult.[122]

In a structure with this level of collaboration it is important to ensure that interests of different stakeholders are considered and respected through the course of treatment development. These players, including pharmaceutical companies, academic institutions, hospitals, and government regulatory agencies, have different institutional cultures which can hinder cooperative efforts. Misaligned or different goals can lead to issues regarding intellectual property, publication policy, conflict of interest, antitrust, or rewards. Perhaps even more harmful is an "insular" system in which the movement of ideas and information is restricted which may also have severe consequences on the timeline of drug development.[123]

One way to incentivize development is by providing increased funding for coordinated efforts that are composed of teams from different organizations and disciplines.[124] Following the model created by Stand Up To Cancer (SU2C) and creating these types of agencies specifically for pediatric oncology which replicate this methodology can entice innovation and collaboration. SU2C provides the "Dream Team" grant to multi-institutional groups of scientists who are working together rather than competing and the "Innovative Research" grants to cancer research projects which are high-risk but also high-impact. The actual funds are managed by the American Association for Cancer Research (AACR) while grant management and allocation is

[121] LoRusso, Patricia M., et al. "Accelerating cancer therapy development: the importance of combination strategies and collaboration. Summary of an Institute of Medicine workshop." *Clinical Cancer Research* 18.22 (2012): 6101-6109.
[122] Bozic, Ivana, et al. "Evolutionary dynamics of cancer in response to targeted combination therapy." *Elife* 2 (2013): e00747.
[123] LoRusso, 2012
[124] LoRusso, 2012

controlled by a committee of clinical investigators, physicians, and other experts in the field.[125] Because the grants are primarily for translational research, delineating funds specifically for collaborative efforts or high-risk/high-reward endeavors in childhood cancer can incentivize the development of new drugs for children during this time of severe shortage.

Establishing a multisite clinical trial can take years and new scientific developments may already have occurred in that time. During the creation of these trials, each institution must receive Institutional Review Board (IRB) approval independently which poses a major time limitation. Ensuring that each participant is presenting a strong trial concept initially to the IRB and frequent communication between all parties may accelerate the approval process.[126] Another method of expediting the process could be by establishing a system in which all institutions receive approval for pediatric cancer trials at once. This would be feasible in the field of pediatric oncology because previous trials will have involved the same players and the trial will be led by one large institution serving as the hub for coordination. Earlier involvement of the FDA in pre-IND (Investigational New Drug) trials, especially when combination therapies are being tested, can prevent later regulatory issues.

Precompetitive collaboration, or collaboration between companies, has been identified as a promising method to make drug development more efficient and create value in the biomedical industry. Collaborative approaches in industry are becoming a necessity as development complexity and costs keep increasing, and it is very rare for one company to have the resources to address the mechanisms by which cancer cells gain resistance to treatment.[127] Precompetition and noncompetition is especially useful in compounds which act on the same molecular target or

[125] "The SU2C Research Model." *Stand Up 2 Cancer*, 2016, http://www.standup2cancer.org/the_su2c_research_model
[126] LoRusso, 2012
[127] LoRusso, 2012

complementarily affect the same pathway.[128] In theory, pre-competitive collaboration allows competitors to pool resources and intellectual property to improve the emergence of new technologies and address industry-wide problems. Historically, governmental agencies such as the NIH, FDA, and NSF have assisted in the creation of pre-competitive consortia and collaborations for their respective fields.[129] A major motivator for precompetitive collaboration in the pharmaceutical industry is the fact that medical innovation and drug discovery requires an understanding of increasingly complex biology.[130]

The TransCelerateBioPharma initiative has been an example of a successful precompetitive partnership, consisting of fifteen pharmaceutical companies, including AstraZeneca, Merck, Amgen, and Pfizer. TransCelerate was launched as a nonprofit in 2012 and has launched a subsidiary to increase efficiency in preclinical research as well as many initiatives which streamline the trial process and make it uniform for participating organizations.[131] AstraZeneca and Merck also successfully collaborated in the development of a combination therapy for cancer, with each player contributing a therapeutic agent. AstraZeneca had developed an agent to block the MEK cellular pathway while Merck had developed one for the Akt pathway; both are important signaling pathways in carcinogenesis and each can act as a backup for the other. Especially when there is only a 5% success rate for anticancer agents in the drug development pipeline, and lower for pediatric cancers, precompetitive collaboration should be pursued to address the growing complexity of cancer biology.[132] Besides making drug

[128] Vassal, 2013
[129] Contreras, Jorge L., and Liza Vertinsky. "Pre-Competition." (2016).
[130] Wagner, J. A. "Open-Minded to Open Innovation and Precompetitive Collaboration." *Clinical Pharmacology & Therapeutics* 87.5 (2010): 511-515.
[131] "Initiatives." *TransCelerateBioPharma, Inc.,* 2016, http://www.transceleratebiopharmainc.com/
[132] Patlak, 2010

development faster and less risky, precompetitive collaboration fosters creative thinking, brings scientists of various backgrounds together, and sparks innovation.[133]

Pediatric oncology institutions in the United States may benefit from using aspects of the franchise-based database model used by the International Cancer Genome Consortium. Because the members are so fragmented, information needs to be integrated and made available to the public. Each member copies its tumor analysis results into a local franchise database, all of which have the same schema to describe tissue samples, clinical information, and genome categorization data. The primary data files are sent to the US National Center for Biotechnology Information (NCBI) or the European Bioinformatics Institute (EBI) while interpreted data sets are stored in franchise databases. A data coordination center has been created to manage the data flow.[134] The application of this model and the creation of a specific data coordination center can be applied to the Children's Oncology Group so that there is greater information sharing between pediatric trials as well as a larger flow of data from adult trials to pediatrics.

4.5 Sustaining Growth in Pediatric Oncology

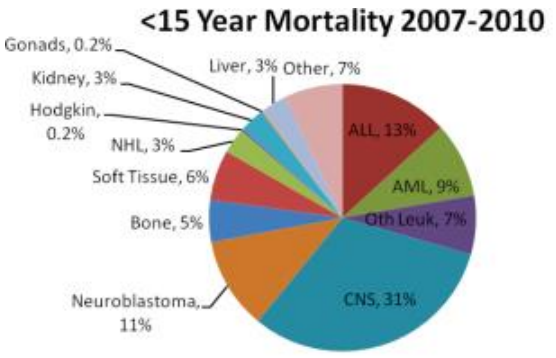
Treatment of childhood cancer has been one of the success stories of medicine in the 20th century. Despite these successes, by the turn of the century slightly greater than 20% of childhood cancer patients still died because of their disease and those that survived faced significant long-term effects. Additionally, different cancer subtypes have faced unequal growth as hematologic malignancies have had a much larger rate of progress than in solid tumors. Acute lymphoblastic leukemia, acute myeloid leukemia, and non-Hodgkin lymphoma have contributed

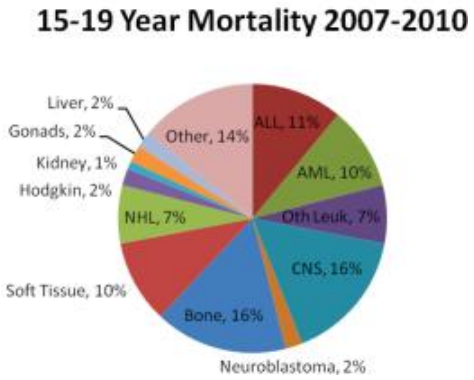
[133] Balogh, Erin, Sharyl J. Nass, and Margie Patlak, eds. *Extending the Spectrum of Precompetitive Collaboration in Oncology Research: Workshop Summary*. National Academies Press, 2010.
[134] Hudson, 2010

the most to improved survival rates.[135] In contrast, progress has been very limited in certain cancers, including high-grade gliomas and metastatic sarcomas. For example, there currently is no effective treatment for diffuse intrinsic potine glioma which has a 9-month median survival and expected death within 18 months.[136]

Patterns of mortality are significantly different between adolescents (15 – 19 years of age) and younger children (<15 years of age). Studies by Smith, et al. which examined mortality patterns between 2007 and 2010 revealed that brain tumors, neuroblastomas, and leukemias accounted for 71% of cancer-related mortality in the younger children, but only for 46% in the adolescents. One-third of mortality in adolescents could be accounted for by bone and soft tissue cancers and Non-Hodgin's Lymphoma, but these cancers cause less than one-sixth of the deaths in younger children.[137] Addressing these disparities and developing treatments based on these trends is integral to lowering mortality rates among all age groups and cancer subtypes.

[135] Pritchard-Jones, K., & Hargrave, D. (2014). Declining childhood and adolescent cancer mortality: great progress but still much to be done. *Cancer*, *120*(16), 2388-2391.
[136] Kearns, 2014
[137] Smith, 2014





It is important to note, however, that while there are differences in the causes of cancer-related mortality between children and adolescents, adolescents have also seen impressive improvements in survival despite their much lower participation in clinical trials compared to younger children.[138] Adolescents (ages 15-19) are often viewed as residing in a "no-man's land" between childhood and adult cancers, and a major reason for their low participation in clinical protocols is low awareness that cancers occur within this age group. While most adolescents are treated at adult facilities, 60 – 75% of their cancers are actually typical of those in the pediatric age range. Their treatment should therefore be determined not by their age but by the type of tumor, whether it shows characteristics of "adult" or "pediatric" tumors.[139] This method would not only improve their chances of survival but also increase participation in clinical trials and

[138] Fern, Lorna A., and Jeremy S. Whelan. "Recruitment of adolescents and young adults to cancer clinical trials—international comparisons, barriers, and implications." *Seminars in oncology*. Vol. 37. No. 2. WB Saunders, 2010.
[139] Ferrari, Andrea, and Archie Bleyer. "Participation of adolescents with cancer in clinical trials." *Cancer treatment reviews* 33.7 (2007): 603-608.

increase the potential number of patients that can be integrated into pediatric trials. The additional recruitment of patients from the adolescent age group may in fact improve research methods and clinical protocols for both adolescents and younger children.

Rare pediatric tumors make up 10% of all childhood cancers and their diverse histologies and clinical characteristics have made them difficult to be thoroughly researched. The number of children with these cancers is so low that these diseases are not included in current registries or treatment protocols.[140] Different entities define rare pediatric cancers in different ways, and there is no uniformly accepted definition within the realm of pediatric oncology.[141] The European Cooperative Study Group for Pediatric Rare Tumors defines it as a cancer with an incidence rate of ≤ 2 per million per year, not considered in clinical trials, or both. Therefore, a cancer with a lack of registries and trials would be considered rare regardless of its incidence rate, such as pediatric melanoma.[142] The COG, in contrast, utilizes a histological approach and defines rare cancers as "other malignant epithelial neoplasms and melanomas." An international collaborative endeavor to reach a consensus on the definition can improve policy and research efforts towards this under-adressed group of cancers.

Improvements in 5-year survival rates have not been uniform amongst all childhood cancers. Children with high-risk neuroblastomas have a 5-year survival rate of less than 50%. Outcomes are also poor in patients with soft tissue sarcomas and malignant bone tumors that have spread beyond their primary site. Low prognosis in these fields demonstrates a need for new therapies and treatments.[143]

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[140] Pappo, Alberto S., et al. "Rare tumors in children: progress through collaboration." *Journal of Clinical Oncology* 33.27 (2015): 3047-3054.
[141] Pui, Ching-Hon, et al. "Redefining" rare" in paediatric cancers." *The Lancet. Oncology* 17.2 (2016): 138.
[142] Bisogno, G., et al. "Rare cancers in children–the EXPeRT initiative: a report from the European Cooperative Study Group on Pediatric Rare Tumors." *Klinische Pädiatrie* 224.06 (2012): 416-420.
[143] "An Analysis"

Neuroblastoma (NB), for example, occurs in very young children with a median age of diagnosis at 17 months. Although neuroblastomas only account for 5% of all pediatric cancer diagnoses, they account for 10% of all childhood mortalities.[144] While a number of different therapies are being developed to treat this disease, molecularly targeted agents are seen as the most promising strategy. Even though the agents have individual promise, the greatest potential lies in combination therapies. As a result, most phase II studies in NB use an experimental agent in combination with a chemotherapeutic backbone. To fully take advantage of these developing therapies different mechanisms will need to be developed to and different suggestions have been made to improve therapeutic outcomes.

Personalizing the approach towards targeted therapies poses one of the most significant challenges but could offer a high benefit in outcome improvement. Specific genetic mutations in NB are rare but identifying certain mutations in protein inhibitors could be used to predict response to therapies. The issue in this domain is integrating such testing into routine clinical management. Doing so will require greater communication and work between researchers identifying mutations and pediatric oncologists. Not all targeted therapies have readily available predictive biomarkers and as such there is currently no way to predict response to a certain agent and inform on therapy choice in cases of relapse.[145] One method to overcome this problem would be to create profiles of specific tumors using DNA sequencing, gene expression arrays, and phospho-proteomics.[146] Such a profile could be used to identify which molecular signaling pathways have been activated and therefore provide information on which specific molecular

[144] Smith, Malcolm A., et al. "Outcomes for children and adolescents with cancer: challenges for the twenty-first century." *Journal of Clinical Oncology* 28.15 (2010): 2625-2634.
[145] Morgenstern, Daniel A., Sylvain Baruchel, and Meredith S. Irwin. "Current and future strategies for relapsed neuroblastoma: challenges on the road to precision therapy." *Journal of pediatric hematology/oncology* 35.5 (2013): 337-347.
[146] Gustafson WC, Matthay KK.Progress towards personalized therapeutics: biologic- and risk-directed therapy for neuroblastoma. Expert Rev Neurother. 2011;11:1411–1423.

agent would be the best choice in inhibiting those pathways. Especially in cancers with a high rate of relapse, such as NB which has a rate of close to 50%, molecularly targeted agents may offer the chance if not to cure the disease, then at least to manage it and transform it into a chronic instead of fatal disease.

In these types of Phase II studies, however, patient selection criteria will become especially important as the molecular targeted therapies may only affect those with a specific molecular phenotype while the overall group of participants may not see significant improvements. This may lead to a therapy being abandoned prematurely. Especially given the low number of children diagnosed with NB, in order to adequately select patients for phase II trials researchers and clinicians may have to establish international response criteria.[147]

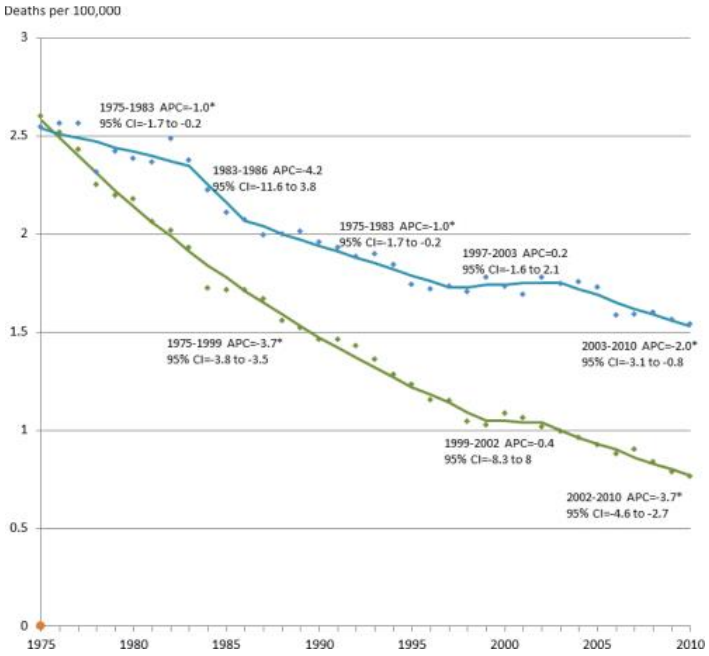
Improving treatment success for rare pediatric cancers is most likely to improve through increasing the referral base for trials of these tumors. Trial recruitment is not the only issue as there is a serious lack of understanding of the biological characteristics of these tumors. Therefore, there needs to be greater access to tissue samples, registries, and patient data on a national and international level. While partnerships, for cancers such as melanoma, with adult groups have not proven successful due to infrastructure and funding limitations, collaboration should continue to better translate treatment options for children.[148]

Over the last decade many have claimed that conventional anti-cancer treatments have been optimized in high-income countries as the rate of decrease in mortality has been slowing since the early 2000s[149] and that minimal improvements are possible moving forward.[150] While survival rates for some cancers such as leukemias and lymphomas have continued to improve

[147] Morgenstern, 2013
[148] Pappo, 2015
[149] Pritchard-Jones, 2013
[150] Pritchard-Jones, 2014

over the last fifteen years, the declines in mortality have slowed by approximately 2% every year. Furthermore, 5-year survival rates for solid tumors other than neuroblastomas, especially sarcomas, have not changed in the last 15 – 20 years, and there have only been modest improvements in brain tumor survival.

The improvement in outcome for children with cancer has closely paralleled the organizational developments and transformations of the pediatric oncology field. The initial formation of the COG and the period of peak activity of cooperative multicenter clinical trials groups were times which saw the greatest growth in outcome. The decreases in mortality rates are also closely correlated with the times of intense focus on exploring multimodal therapeutic approaches, which eventually developed into the standards of care for the disease.[151]



However, long-term effects of cancer therapies also need to be taken into account. Being cancer free does not equate to being free of cancer's effects. Survivors often face significant medical and psychological complications later in their life, and therapies which lessen the

[151] Reaman, Gregory H. "Pediatric cancer research from past successes through collaboration to future transdisciplinary research." *Journal of Pediatric Oncology Nursing* 21.3 (2004): 123-127.

occurrences of these side effects should continue to be pursued, regardless of its curative traits. Drugs which achieve the same, if not improved, therapeutic results with less toxicity and more molecularly targeted pathways should be the ultimate goal. Childhood cancer survivors are expected to live many years beyond their treatment and the side-effects o treatment can take many years to manifest themselves, preventing survivors from fully achieving their potential.[152] These long-term risks can include a second cancer diagnosis, chronic health conditions such as myocardial infarctions, neurocognitive defects, and psychosocial effects of their disease and treatment.[153]

Psychosocial and behavioral studies in cooperative group research have overlooked many topics and represent a potential area for growth and development. Within cooperative clinical group trials, the primary focus of psychosocial behavioral research has been on the neurocognitive consequences of treatment. Here, there is an opportunity to further evaluate phenomena such as family dynamics during the cancer experience, remedial interventions of learning disabilities, assessments of child and family function, and methods to decrease aversion to treatment because of pain and discomfort. Individual researchers have taken the lead on evaluating quality of life, coping, and psychosocial functioning in these patients but the cooperative infrastructure of pediatric oncology offers further avenues of research.

Multi-institution studies would allow access to large numbers of children with similar diseases and treatment, because of the uniformity in protocols across consortium participants, and therefore create more significant results. Studies performed within the same institutions usually include children with different cancers undergoing a variety of treatments, including modes of therapy, which reduces the statistical power of such studies. Large clinical trials offer

[152] Pritchard-Jones, 2013

[153] Oeffinger, Kevin C., Ann C. Mertens, and Charles A. Sklar. "Chronic health conditions in adult survivors of childhood cancer." *Oncology Times* 29.1 (2007): 26.

opportunities to understand correlative links between biological, genetic, and clinical data and psychosocial phenomenon. This can help understand associations which improve treatment efficacy, reduce toxicity, and improve quality of life. Incorporating these types of studies within cooperative groups also offers access to enrolling and tracking participants over a large number of years. There is an emerging emphasis on the later consequences of disease and treatment and cooperative trial participant databases would enhance such data collection and understanding.[154]

[154] Reaman, 2004

5 Expansion to Other Diseases and Fields of Medicine

The accomplishments of pediatric oncology hold valuable potential for applications to adult oncology. There are many characteristics of the pediatric cancer model which could transform care in adult patients and greatly improve outcomes if it were to be applied in a judicious and strategic manner. Applying some of the collaborative traits of childhood cancer to adult cancer could serve as the catalyst for overcoming the current roadblocks to progress or stagnation in advancement.

The collaborative model of pediatric oncology could be applied to any field of medicine to yield improved results. While pediatric oncology clearly has elements which could be easily translated to adult oncology to bring improvements, it can also serve as a model for other fields of medicine. The lessons and successes of this model can lead to innovations in therapy, improved delivery of healthcare, better patient experiences. First, areas of growth within adult oncology will be discussed. Next, categories of diseases which could benefit from a collaborative treatment and research model will be discussed. Finally, Alzheimer's, a relatively common disease with high levels of funding but little biological understanding, will be explored as a non-oncological case study for collaboration expansion.

5.1 Expansion to Adult Oncology

The collaborative model established in pediatric oncology has the potential to transform the nature of care and success in the field of adult oncology. Five-year cancer survival rates for adults are higher now than at any time in the past and cancer incidence rates are also decreasing.[155] Although mortality rates have declined in every state, the extent to which they have varies in magnitude between different regions of the United States. Between the early

[155] Siegel, 2016

1990's and 2011, declines ranged from 9% in Oklahoma to 33% in the District of Columbia. Generally, Southern states had the slowest declines and highest current death rates while the Northeastern states had much higher declines.[156] Expansion of multi-institutional clinical trials in adult oncology can potentially mitigate these differences by bringing treatments to the smaller centers which are more likely to be found in rural areas. Existing cancer knowledge cannot be applied to all segments of the population if there is no structure to disseminate treatment to individuals who are physically isolated from the large centers where most of the breakthrough discoveries are occurring.

Because the most anticancer drugs are developed for adults, there is not a shortage of sufficient pharmaceutical treatments for treating adult malignancies. However, as the biological understanding of cancer is progressing, it is becoming increasingly apparent that cancers need to be grouped based on their subtype.[157] Until now, adult oncology has been able to pursue successful trials despite the fact that only 3% of patients participate in one at some point in their treatment.[158] As cancers are classified into smaller and smaller groups, the same issue of number of trial participants that is found in pediatric oncology rises. "Common cancers" are increasingly becoming fragmented into smaller molecular subsets, and therefore substantially increasing the number of rare cancers.[159] In order to reach sufficient numbers for phase II and phase III of the trials, hospitals, research institutes, and pharmaceutical companies will need to collaborate.

The creation of a consortium to oversee trials could also be extremely beneficial. While creating one consortium for all cancers would likely be unfeasible and ineffective, having an organization serve as an overseer for all breast cancers or all blood cancers would likely increase

[156] Siegel, 2016
[157] Rioux, 2016
[158] "Pediatric Clinical Trials"
[159] Billingham, Lucinda, Kinga Malottki, and Neil Steven. "Research methods to change clinical practice for patients with rare cancers." *The Lancet Oncology* 17.2 (2016): e70-e80.

the rate of treatment development. A consortium of this type would be able to bridge barriers between the numerous academic and clinical institutions.

Furthermore, a replication crisis has been identified in biomedicine due to weak experimental designs, contamination, and sloppy data analysis.[160] A study performed in 2015 found that over 50% of preclinical research was irreproducible, resulting in a waste of over $28 billion.[161] Following the model created by PPTP and having one organization perform preclinical identification of treatments by providing access to a variety of tumor samples could be very effective. A consortium would act essentially as a supervisor by creating uniform standards, aligning stakeholder priorities, and standardizing procedures and, as a result, address much of the inefficiency and weaknesses of the system. As cancers are increasingly fragmented, the number of trials could also increase inefficiently with overlap occurring. Especially when the cost of research is already increasing substantially, there needs to be enhanced communication, both nationally and internationally, to promote group efforts rather than waste resources on multiple trials addressing the same topic.[162]

The well-established integration of the interdisciplinary team and the fact that it is an expected part of treating cancer is not a phenomenon present in adult oncology. The concept of team-based care already exists within oncology, known as the multidisciplinary care team (MDT) which was based on the tumor board, but is composed of physicans of different specialties. Additionally, oncology care within these teams is not coordinated and the burden of

[160] Engber, Daniel. "Cancer Research Is Broken." *Slate. com, April* 19 (2016), http://www.slate.com/articles/health_and_science/future_tense/2016/04/biomedicine_facing_a_worse_replication_crisis_than_the_one_plaguing_psychology.html

[161] Freedman, Leonard P., Iain M. Cockburn, and Timothy S. Simcoe. "The economics of reproducibility in preclinical research." *PLoS Biol* 13.6 (2015): e1002165.

[162] Blay, 2016

doing so often falls on the patient.[163] A change which would perhaps have the most direct impact on the lives of patients is a greater incorporation of multidisciplinary treatment into adult oncology. Integrating counseling services into cancer treatment and establishing it as common practice would be especially important in providing patients with the mental support during an extremely vulnerable time. Many patients still do not receive adequate psychosocial care[164] despite numerous studies outlining the need for such services.

While providers may interact dynamically, they do not always work interdependently or adapt to achieve common goals. The team may share the same goal of improving the health of the patient but personal and professional goals, hierarchal rigidity, and incomplete information as the patient moves between providers may impede collaboration. In reality, adult oncological care is provided by a team of teams which only increases the potential for inefficient, uncoordinated, and sometimes suboptimal care.[165]

When expanding the role of teams and collaborative care within adult oncology the importance of organizational environment should not be forgotten. The organization in which the team resides must also be able to support teamwork, this includes supporting, reinforcing, measuring, and developing team-based behaviors and attitudes. The cancer care team cannot excel without optimal organizational conditions.[166] Although it may have room for improvement on this front, pediatric oncology institutions have fostered teamwork. Translating the

[163] "NCI-ASCO Teams in Cancer Care Delivery Workshop." *American Society of Clinical Oncology,* February 2016, https://www.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/2016-NCI-Teams-Kosty.pdf

[164] Fann, Jesse R., Kathleen Ell, and Michael Sharpe. "Integrating psychosocial care into cancer services." *Journal of Clinical Oncology* 30.11 (2012): 1178-1186.

[165] Kosty, Michael P., et al. "National Cancer Institute–American Society of Clinical Oncology Teams in Cancer Care Project." (2016): JOPR018127.

[166] Salas, Eduardo. "Team Science in Cancer Care: Questions, an Observation, and a Caution." (2016): 972-974.

collaborative model to adult oncology will require that the organizations and institutions of that field provide the same environmental support.

Because expanding the use of collaborative teams would be a dynamic change, patient advocates should be to not only ensure a focus on patient voices but also to help facilitate teamwork. Patient advocates bring in the viewpoints, needs, and concerns of patients into the teams comprised of clinicians, researchers, and other healthcare professionals. The patient advocate ensures a patient-centric approach as the managerial aspects of providing healthcare undergo changes. One large barrier to effective teamwork within and between organizations is incompatible Electronic Health Records (EHRs). Even when the EHR system is less than ideal, patient advocates can serve as a point of communication between the different institutions.[167]

Within adult populations, increasing the disciplinary diversity of oncology teams can not only allow comprehensive care of the whole patient but also address barriers to care. Different disciplines have different approaches to asking an adult patient about their cancer and interpreting that information. Consequently, when these perspectives are combined, medical and nonmedical barriers to care may be identified. Such barriers may have cultural, financial, or psychosocial, socioeconomic, or health literacy bases.[168] Especially when patients of different cultural and socioeconomic backgrounds come to receive treatment, disciplinary diversity can improve the healthcare they receive.

One cause of this may be a larger societal issue of not addressing mental health issues and stigmatizing those who may be mentally troubled. Perhaps the system does not provide a mandate for this type of mental health support in an effort to respect the wishes of adults, who

[167] Lederman, Lynne, et al. "Patient Advocates Collaborate to Ensure Patients Are Members of Their Own Oncology Care Teams." (2016): 980-982.
[168] Parsons, Susan K., et al. "Promoting High-Quality Cancer Care and Equity Through Disciplinary Diversity in Team Composition." *Journal of Oncology Practice* 12.11 (2016): 1141-1147.

presumably would be able to articulate a desire for such services, and not force unwanted treatment. These services are not provided as an option to children; they are integrated into the treatment plan, partially because pediatric oncology treatment focuses much more on quality of life after survival than adult oncology. Currently, the professional standards of the Commission on Cancer mandate that all cancer patients must be screened at least once for psychosocial distress. While heightened awareness of this issue is a step in the right direction, psychosocial support services should be a well-integrated aspect of care from the onset of treatment and not only a crisis management mechanism. As survival rates for adults are increasing and the field is increasingly addressing survivorship-related issues, providing more and better psychosocial services will be key in improving health outcomes.

Pediatric oncology can also inform on other aspects of treating adult oncology. The focus of care in pediatric oncology always includes the family and treatment centers are staffed and physically set up to address the needs of parents and siblings in addition to the patient's. In the adult setting, families and friends have begun to play a larger role in an individual's treatment yet they are not given the same resources and support for doing so. Especially when cancer care is provided in an outpatient realm the needs of families and friends are increasingly under supported.[169] It is clearly known that social support plays an integral role in coping with illness and improving health outcomes [170] and the health delivery system ought to assist in the needs of an individual's social network.

When treating children, pediatric oncologists are very cognizant of the developmental effects chemotherapy or the therapies may have. There is a significant amount of focus placed on potential adverse effects to other organs as well as potential intellectual and emotional

[169] Rowland, Julia H. "Foreword: Looking beyond cure: Pediatric cancer as a model." *Journal of Pediatric Psychology* 30.1 (2005): 1-3.
[170] Bloom, Joan R. "The relationship of social support and health." *Social Science & Medicine* 30.5 (1990): 635-637.

development. These functional outcomes receive much less attention in the adult setting. Simply starting treatment takes precedence over considerations regarding fertility, family, work and social roles, and economic situations. As a result, it often becomes too late to take advantage of late-effect considerations, such as sperm or ovarian tissue banking.[171] While traditional oncologists may not address these issues early enough, integrating a multidisciplinary team could bring earlier focus to late-term developmental consequences to the benefit of the patient.

As described earlier, pediatric oncology treatments take note of the patient's age as well as current and future functional status simply because they are expected to live longer and remain members of society. Consequently, when new information regarding the adverse effects of treatment becomes available, changes in standard therapy are made very quickly, partially because of the centralized and well-organized consortium approach. In the adult setting, however, oncologists often make recommendations without considering the patient's potential life span, preferences, or potential for an active lifestyle. The aging population is becoming healthier and patients are increasingly requesting therapies which maintain the ability to pursue life goals and meaningful activities. Adult oncologists, therefore, ought to utilize research on quality-of-life outcomes more.[172]

As morose as it may seem, the traditional viewpoint has been that oncology patients of a higher age simply do not have as much time left to pursue goals, maintain an active lifestyle, or contribute to society. With changes in technology and overall health status, this perspective needs to evolve in conjunction with the demographic shifts that are occurring. Leading meaningful lives after treatment is increasingly becoming a possibility for middle-aged and older

[171] Rowland, 2005
[172] Rowland, 2005

patients, and there ought to be greater efforts to maintain a high quality of life both during and after treatment.

From a societal standpoint there seems to be a greater ease in dedicating greater resources to the pediatric patient, both because they have their whole life ahead of them and investing in their survival is a smart choice and also because these children have no personal responsibility in their diagnosis. For many adult patients, cancer may have been caused by poor lifestyle choices and spending large amount of money on them sometimes seems less justifiable, especially when they have fewer years left to live. However, society has already invested in these adults in a variety of ways for a long amount of time and so providing better cancer care may be a way to ensure the earlier investments are not lost. Additionally, many of the reasons for poor lifestyle choices may be caused by societal inequalities rather than individual choice and every member of society ought to receive the best medical care possible regardless of their previous conditions.

Finally, pediatric oncologists understand the long-term challenges a family and patient can face years after treatment has been completed. These patients require long-term follow up care and the pediatric community is exploring which types of physicians should be overseeing this process. Even though this exists in the adult realm, the subsequent physicians are often primary care doctors who are less familiar than oncologists on the late effects of cancer treatments. Non-oncology specialists may not understand how treatments were given years ago and may not know the long-term psychosocial, genetics, and applied therapy risks. As children transition into adulthood and begin seeing a different type of provider, such lack of informational knowledge becomes more pressing.[173] Adult who are childhood survivors of cancer often do not remember the details of their treatment, such as the different therapies they received and their

[173] Rowland, 2005

long-term risks, and this lack of knowledge can lead to suboptimal long-term care.[174] The Children's Oncology Group is currently working to establish a treatment summary form which would be provided to patients and their families at the end of treatment. Expanding this model into adult practice could improve the follow-up care of survivors of all ages so that their health care providers can discuss, design, and deliver the best possible care.

5.2 Lessons for Other Diseases

It is clear that greater collaboration in a variety of field of medicines would lead to improved outcomes and greater innovation in therapies. However, certain diseases and areas may be more conducive to the pediatric oncology model because of the conditional similarities they share with the disease. These similar diseases have an untapped potential for large growth and development in scientific understanding, treatment, and long-term survivorship.

There are certain characteristics which may make a disease more apt for introduction of greater teamwork and coordination. One, having large amounts of research funding and a public willing to donate significantly to the disease would incentivize the creation of a consortia approach. While childhood cancers may not receive as much pharmaceutical attention, much of the early growth in the field happened because individuals and society were willing to donate large sums of money to uncover the scientific principles of the disease. Other childhood diseases and Alzheimer's, for example, have a high allocation of resources and could benefit from collaboration.

This leads to a second characteristic of having limited scientific understanding of the principles underlying the disease, either caused by low incidence numbers or just general lack of knowledge. The first breakthrough success in pediatric oncology was in ALL and occurred

[174] Kadan-Lottick, Nina S., et al. "Childhood cancer survivors' knowledge about their past diagnosis and treatment: Childhood Cancer Survivor Study." *Jama* 287.14 (2002): 1832-1839.

because researchers were desperate to make some sort of progress and stumbled upon multimodal therapies as highly effective therapeutic agents. Coordinated trials and research collaboration among the public and private sectors could facilitate a more rapid pace of development in diseases such as Alzheimer's. Rare diseases with low incidence numbers in both children and adults, such as Neglected Tropical Diseases (NTDs), have been shown to benefit from coordination of research to enhance trial participation.

Alternatively, if a disease lacks sufficient financial allocations then having an infrastructure which improves communication between different research entities would lead to a more efficient use of resources. Diseases such as alcoholism or conditions like migraines do not receive sufficient funding and therefore are under-researched because of social stigmas or misconceptions. Creating a system which allows for the sharing of data and results would capitalize the work that is being done. While this may be difficult given the competitive nature of research and the publish-or-perish phenomena, incentives for collaboration can be implemented at a low cost.

Chronic diseases with no cure have already been shown to benefit from an interdisciplinary and collaborative treatment model. Patients with depression, diabetes, and coronary heart disease have faced significantly improved outcomes when treated with a collaborative care model and a medically supervised nurse.[175] Other chronic diseases such as Crohn's and Inflammatory Bowel Disorder which not only require management of multiple symptoms but as of yet have few promising therapies have the potential to undergo large transformations in growth.

[175] Katon, Wayne J., et al. "Collaborative care for patients with depression and chronic illnesses." *New England Journal of Medicine* 363.27 (2010): 2611-2620.

Finally, patients who have been diagnosed with diseases with intense treatment, long-term survival, and psychosocial consequences could be greater supported through the integration of multidisciplinary care. Providing psychological care to child cancer patients and having social workers and patient navigators work with families decreases the burden of the disease and supports the patient in living a meaningful life with as few long-term effects as possible years after completion of treatment. Making these types of services standard of practice in other diseases with deep psychological impact and long-term expected survival would improve the patient experience and lead to an overall improvement in health outcomes.

5.3 Alzheimer's: A Case Study

Alzheimer's is a degenerative brain disease and is the most prevalent cause of dementia. It includes pathologic changes in the brain prior to the beginning of symptoms as well as the disease itself. Symptoms of Alzheimer's include difficulty remembering, names, conversations, or events, apathy and depression, impaired communication, confusion, poor judgement, behavior changes, and difficulty performing everyday tasks such as speaking or walking. The accumulation of beta-amyloid plaques outside the neuron and tau protein buildup inside causes destruction of neurons.[176] 40 million individuals worldwide have Alzheimer's and this number is expected to double every 20 years.[177] In 2017, 5.5 million Americans are living with the disease.[178]

Most Alzheimer's patients receive treatment for their care from general physicians and increasing collaborative care within these environments can significantly improve Alzheimer's treatments outcomes. Utilizing an interdisciplinary team led by an advanced practice nurse has

[176] "2017 Alzheimer's Disease Facts and Figures." *Alzheimer's Association, 2017,* http://www.alz.org/documents_custom/2017-facts-and-figures.pdf
[177] Prince, Martin, et al. "The global prevalence of dementia: a systematic review and metaanalysis." *Alzheimer's & Dementia* 9.1 (2013): 63-75.
[178] "2017 Alzheimer's Disease"

been shown to significantly improve quality of care and the behavioral and psychological symptoms of patients. These patients had fewer symptoms of dementia and improvements in depression, without a significant increase in the use of antipsychotics or sedative hypnotics.[179] Given the severity of symptoms of this disease and the high burden placed on caregivers, such significant improvements should be translated into practice.

Alzheimer's has staggering socioeconomic costs with an estimation of $604 billion worldwide.[180] Current therapies only address symptoms and only provide limited benefits to patients[181], contributing to a significant need for the development of novel and more effective therapies. Recent late-stage drug failures in phase III trials have indicate a need for innovation within the research model for Alzheimer's. Increasing collaboration between academia, industry, and government at the mechanistic understanding level, allowing for precompetitive information sharing, and creating a multi-institutional funding model can lead to greater growth.

At later levels of drug development, a collaborative research network could provide the opportunity to standardize disease models, establish biobanks, and create a framework for data sharing. There are large gaps in understanding the underlying mechanisms of the disease which could be addressed through cooperative research. Identifying biomarkers for Alzheimer's can have transformative effects on treatment, as was seen in pediatric oncology. Novel, precompetitive trials, which would reduce risk because it would be funded by all shareholders, have been identified as a method to test drugs and diagnostics collaboratively.[182] Rather than

[179] Callahan, Christopher M., et al. "Effectiveness of collaborative care for older adults with Alzheimer disease in primary care: a randomized controlled trial." *Jama* 295.18 (2006): 2148-2157.
[180] World Health Organization. *Dementia: a public health priority*. World Health Organization, 2012.
[181] Raina, Parminder, et al. "Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline." *Annals of internal medicine* 148.5 (2008): 379-397.
[182] Feldman, Howard H., et al. "Alzheimer's disease research and development: a call for a new research roadmap." *Annals of the New York Academy of Sciences* 1313.1 (2014): 1-16.

creating new initiatives, combining efforts would be a more efficient manner to take advantage of limited funding and resources while providing the greatest benefit for patients.

6 Ethical Considerations

The treatment of cancer care is closely intertwined with the considerations of bioethics; treating children, especially those with serious life-threatening diseases, is wrought with moral and ethical dilemmas. Even though the ultimate goal may be providing medical care in order treat the disease, understanding the ethical foundations of scientific research and medical practice is necessary for good clinical care. Healthcare professionals in this field may find themselves in positions questioning what the "right" path is when families are under high levels of distress, children diagnosed with cancer are extremely vulnerable, and there is a strong commitment to finding a cure. Important ethical issues within this field can include: disclosure, assent, informed consent, and medical late effects.[183] Ethical principles ought to be an important consideration in the treatment of children with cancer in order to provide the most beneficial and morally appropriate care possible.

6.1 Ethical Complications in Decision Making

The moral imperative to pursue pediatric oncology research is strong; after all, cancer kills more children than any other disease. Ethical pediatric treatment is dictated on the principles of beneficence and non-maleficence; that the treatment should be in the best interest of the child. Research, however, also contains the added component of benefit to others and therefore autonomy is the prevailing principle. This principle of autonomy mandates that subjects participate in research voluntarily, with adequate information, and after giving explicit consent.[184] As clinical trials are not only designed to test the efficacy of cancer therapies but also its toxic effects, there are numerous ethical considerations surrounding the participation of

[183] Wiener, Lori, and Anne E. Kazak. *Pediatric Psycho-oncology: A Quick Reference on the Psychosocial Dimensions of Cancer Symptom Management*. Oxford University Press, 2015.
[184] de Vries, 2011

children in research trials.[185] Informed consent is the first step of the process in trial participation and is necessary for a child to be enrolled in a trial.

The close relationship between research and care in pediatric oncology creates challenges for the principle of voluntariness of informed consent of parents for their child's participation in clinical trials.[186] Parents are the principal decision makers for their child's involvement in cancer research as young children have not developed enough to make choices that are fully voluntary, autonomous, and competent.[187] Informed consent for research is often required immediately after diagnosis, and when parents are in shock and disbelief their decision to enroll in research may not be fully intentional, thus not making the consent fully voluntary.[188]

Because minors lack the competence to make informed decisions, their parents serve as surrogate decision makers. The pediatric patient is so dependent on the adult caregiver that they must express their autonomy through others.[189] In fact, the American Association of Pediatrics' Bioethics Committee has declared that the "doctrine of informed consent has only limited direct applications in pediatric oncology."[190] This, of course, raises the question of how surrogates should decide. The best interest standard has been regarded as the best solution to the challenge of substituted judgement. In the best interest standard the surrogates are held to make decisions

[185] Ungerleider RS, Ellenberg SS. Cancer trials: design, conduct, analysis, and reporting. In: Pizzo P, Poplack D, eds. *Principles and practice of pediatric oncology,* 3rd ed. Philadelphia: Lippincott-Raven, 1997:85-408.
[186] Dekking, Sara AS, Rieke Van Der Graaf, and Johannes JM Van Delden. "Voluntary Informed Consent in Paediatric Oncology Research." *Bioethics* (2015).
[187] De Vries et al, *op. cit*. note 1; E.K. Martenson, A.M. Fagerskiold. A review of children's decision-making competence in health care. J Clin Nurs 2008:17:3131–41.
[188] Dekking, 2015
[189] Blum, R. W., & Martin, A. S. Ethical Considerations in Pediatric Oncology: A Case-Based Psychosocial Overview. *Pediatric Psycho-Oncology: Psychosocial Aspects and Clinical Interventions, Second Edition*, 2012: 231-245.
[190] American Academy of Pediatrics Committee on Bioethics. "Informed consent, parental permission, and assent in pediatric practice." *Pediatrics* 95.2 (1995): 314-317.

based on what is best for the child, not what they think is the best choice for themselves, what they would prefer, or what they think the child would want.[191]

Quality informed consent is a bedrock of ethics in research practices. Pediatric cancer phase I trials face unique and multiple ethical challenges, yet many parents whose children participate in phase I trials do not understand the specific purpose of these trials. Upon interviewing parents after informed consent conferences (ICC) between the physician and parents, it was found that only 32% of parents had a substantial understanding of the purpose of phase I trials and 35% demonstrated little or no understanding. Doctors oftentimes also failed to disclose important aspects of medical regimens during these phases, such as drug safety (explained in 23% of ICCs), dose finding (52% of ICCs, and dose escalation (53% of ICCs). This clearly demonstrates an issue in physician-parent communication that needs to be overcome in order to improve quality of care.[192]

6.2 Ethical Implications of Phase I Trials

Phase I trials are perhaps what pose the most ethical dilemmas as they test an agent on human subjects for the first time. The ethical discussion in this area usually centers on the question of direct benefit. Even though meta-analyses have found that there is only a small clinical response rate in Phase I cancer trials, it is also argued that any chance of direct benefit qualifies as "prospect". Here is where the dichotomy between research and clinical medicine becomes significant; the scientific intent of Phase I is to find dosage guidelines but the clinical intent is to provide beneficial medical treatment to the patient.

The first phase of trials contains its own concerns for Phase I studies. Phase I trials expose children to more than minimal risk, and raise the question of whether parents can provide

[191] Blum, 2012

[192] Cousino, Melissa K., et al. "Communicating and understanding the purpose of pediatric phase I cancer trials." *Journal of Clinical Oncology* 30.35 (2012): 4367-4372.

informed consent for such trials given the poor chance of response. Generally, the only alternatives to Phase I trials are palliative care only or continuing failed therapies. However, because there is a very small chance of chance of response the Phase I trial can be considered comparable to the potential benefits from the two alternative options given that the trials are rational and well-designed. [193]

Therapeutic intent must be considered when undertaking participation in a phase I trial because otherwise a child may be unnecessarily exposed to side effects, discomfort, and adverse events which is morally unjustifiable. Because these trials are not curative, determining therapeutic intent becomes more difficult and a thorough risk versus benefit assessment must be made. This risk vs. benefit analysis is critical in maintaining the principal of beneficence, which is defined as an obligation to do no harm while maximizing benefits and minimizing risks. These trials may, however, provide benefits through symptom relief, disease stabilization, and even maintenance of hope. The preliminary studies may be the last remaining treatment option and families may view the potential for any type of benefit, however rare it may be, as advantageous. While those who participate in these trials may not receive direct benefit, it will inform future patients. Given the ethical dilemma surrounding phase I trials, it is essential that families and patients are communicated with directly and clearly. They must be given and understand all possible options in order to make a fair and just decision.[194]

6.3 Palliative and End of Life Care

The current state of oncological care has seen a massive shift towards increasingly aggressive treatment that does everything which is possible. Based on reports from surrogates

[193] Barfield, Raymond C., and Christopher Church. "Informed consent in pediatric clinical trials." *Current opinion in pediatrics* 17.1 (2005): 20-24.
[194] Haylett, Wendy J. "Ethical considerations in pediatric oncology phase I clinical trials according to The Belmont Report." *Journal of Pediatric Oncology Nursing* 26.2 (2009): 107-112.

and patients the number of patients receiving "all care possible" increased from 7% in 2000 to 58% in 2012, representing an increase by a factor of eight.[195] While this data stemmed from adult patients, cancer treatment overall is becoming more aggressive.[196] The National Cancer Board has already indicated that overly aggressive treatment may represent "poor quality care" as underuse has traditionally been focused on as a source of poor quality care and not overuse.[197]

Even though pediatric cancer patients face vastly different outcome potentials and demonstrate greater resilience to treatments, the value of palliative and end-of-life care should not be ignored. Palliative care is given to improve quality of life and help manage symptoms associated with the disease, including pain. The goal of palliative care is not to cure but rather to prevent or treat the symptoms and side effects associated with the disease and its treatment.[198] It also addresses the physical, emotional, psychological, and spiritual needs of the patient compassionately. Today, there is a greater understanding of the value of providing palliative care and professional institutions such as the Commission on Cancer and College of Surgeons have mandated that palliative services be a component of the patient's treatment.[199] However, this resource should be used from the beginning of treatment and not only in instances of crisis.

Hospice in, in contrast, is directed towards those in the terminal stages of their cancer or with a terminal prognosis. While it encompasses many of the same principles of palliative care, Hospice focuses more on improving quality-of-life, promoting decision making in the end-of-life

[195] Narang, Amol K., Alexi A. Wright, and Lauren H. Nicholas. "Trends in advance care planning in patients with cancer: results from a national longitudinal survey." *JAMA oncology* 1.5 (2015): 601-608.
[196] Goodman, David C., et al. "Trends in cancer care near the end of life." *A Dartmouth Atlas of Health Care Brief* (2013).
[197] Earle, Craig C., et al. "Aggressiveness of cancer care near the end of life: is it a quality-of-care issue?." *Journal of Clinical Oncology* 26.23 (2008): 3860-3866.
[198] "Palliative Care in Cancer." *National Cancer Institute,* 2017*,* https://www.cancer.gov/about-cancer/advanced-cancer/care-choices/palliative-care-fact-sheet#q1
[199] "Cancer Program Standards: Ensuring Patient-Centered Care." *Commission on Cancer*, 2016, https://www.facs.org/~/media/files/quality%20programs/cancer/coc/2016%20coc%20standards%20manual_interactive%20pdf.ashx

process and supporting grieving. Due to the Medicaid structure of the United States, Hospice is generally limited to the last six months of a patient's life.[200]

Providing palliative or hospice care should not be viewed as giving up hope. Dying children may seem contrary to the natural order but referral to an end-of-life program should not be translated into failure. Patients diagnosed with invasive cancers who receive palliative care not only have a higher quality of life but also live longer lives.[201] Additionally, it has also been found that terminal patients who receive hospice care live longer than those who do not.[202] While utilizing these services may be viewed as accepting defeat, the reality is that they not only increase length of life but significantly improve its quality. Patients who received aggressive end of life care actually had lower quality of life; therefore while reaching a cure should be a goal, the patient's quality of life should also be prioritized.

Pediatric oncology faces unique circumstances within the realm of end-of-life care. Physicians and other healthcare providers already tend to shy away from difficult conversations surrounding prognosis and treatment due to lack of training, a desire to avoid uncomfortable conversations, and because childhood death is so rare. Furthermore, maintaining communication across different ages, developmental levels, and decision-making capacities is a complex skill set for physicians to master. Professionals who offer end-of-life care to adults, such as hospice staff, also may not have the training to be able to handle the complex psychological, physical, and emotional care of dying children and their families.

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[200] "Palliative or Hospice Care: Does My Child Need This Service?" *American Childhood Cancer Organization,* 2017, http://www.acco.org/palliative-or-hospice-care-does-my-child-need-this-service/

[201] Bakitas M, Lyons KD, Hegel MT, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. JAMA. Aug 19 2009;302(7):741-49.

[202] Connor, Stephen R., et al. "Comparing hospice and nonhospice patient survival among patients who die within a three-year window." *Journal of pain and symptom management* 33.3 (2007): 238-246.

The resilience of children and their ability to recover from situations which may be life-threatening in adults causes providers and patient's families to have different palliative care needs and recurrent end-of-life conversations at different points in time. Clinicians have a notoriously poor ability to predict death, a phenomenon even worse in those living with terminal illness for many years prior to their death. As such, the end-of-life needs of children and their families do not fit well into the medical, psychological, spiritual, and economic system created for adults. While the emotional capacity of each child may be different, they too need to participate to a certain extent relevant discussions and decisions in order to be able to manage and cope with their own grief, say good-byes, and gain some sense of control over their death.[203] While a pediatric cancer patient may not be able to make autonomous decisions in trial participation, they should maintain a stake in their own dying process.

The American Academy of Pediatrics called for integrated care in 2000 in order to provide access to palliative services early in the course of treatment. Despite this, palliative care has been fragmented because of a lack of empirical data of palliative care effectiveness, reimbursement issues, and a lack of palliative care experts.[204] Only 10% of pediatric oncologists formally studied pediatric terminal care, and almost 50% have reported lack of access to a palliative care team.[205] As a result, children and families participating in trials or treatment may not be able to receive access to those services or to information they would need to transition into end-of-life care.

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[203] Hilden, Joanne M., et al. "End-of-life care: special issues in pediatric oncology." *Improving Palliative Care for Cancer. Foley KM, Gelband H, editors; Institute of Medicine and National Cancer Policy Board, Research Council. National Academy Press, Washington, DC* (2001).

[204] American Academy of Pediatrics

[205] Hilden, Joanne M., et al. "Attitudes and practices among pediatric oncologists regarding end-of-life care: results of the 1998 American Society of Clinical Oncology survey." *Journal of Clinical Oncology* 19.1 (2001): 205-212.

Increasing the enrollment of children in Phase I oncology trials would greatly increase the ability of researchers to develop new treatments and improve overall medical care. Especially given the need to develop new anticancer agents which target specific histologic malignancies, due to the high variability in pediatric tumors, more clinical trials will be necessary. One potential way to mitigate the low benefits of Phase I trials could be by integrating it with palliative care. Parents should not have to be forced to choose between trial participation and palliative or end-of-life care. While the research protocol would dictate the management of toxicities in Phase I trials, integrating palliative services into the protocol may augment pain management and other support measures to improve the patient's quality of life.[206]

[206] Ulrich, Connie M., Christine Grady, and David Wendler. "Palliative care: a supportive adjunct to pediatric phase I clinical trials for anticancer agents?." *Pediatrics* 114.3 (2004): 852-855.

7 Significance, Limitations, Future Directions

This paper has chosen to focus on the pediatric oncology model specific to the United States, a prototype which is very similar to that in European countries. There are, however, significant disparities in international treatment methods of pediatric oncology, especially in developing countries which need to be addressed if there is to be equitable treatment for this disease. The dramatic growth in survival rate is a Western phenomenon, and many countries still have low survival rates. 80% of the world's children live in low and middle-income countries (LMICs) and the 200,000 children diagnosed their annually have very limited access to treatment and therapies, and of those only 25% survive. While other diseases such as malaria, diarrhea, and malaria account for a much larger proportion of ailments in these countries, affecting 5 million children annually, there is a still an importance for the treating children with cancer especially when curative therapies occur.[207] Bringing a more stable treatment structure to LMICs would also expand the potential number of children that could be enrolled into clinical trials and thus lead to more significant results and faster research advancements.

Regional collaborative initiatives that work directly with healthcare providers and the population can reach out to almost 60% of children with cancer worldwide. A major challenge over the next few decades will be how to translate the developments made in countries with high levels of resources to children in all geographical locations. There is very little known about the epidemiology of childhood cancers in LMICs and working with local governments to bolster their national registries could lead to important improvements.[208] Improving cancer outcomes in LMICs will require innovative solutions as strategies used in high-income countries cannot be

[207] Kellie, Stewart J., and Scott C. Howard. "Global child health priorities: what role for paediatric oncologists?." *European Journal of Cancer* 44.16 (2008): 2388-2396.
[208] Rodriguez-Galindo, Carlos, et al. "Toward the cure of all children with cancer through collaborative efforts: pediatric oncology as a global challenge." *Journal of Clinical Oncology* 33.27 (2015): 3065-3073.

directly applied there. It will be necessary to move beyond current standards and towards novel methods for finding and applying evidence-based therapies to low-resource settings.[209] While there is clearly area for further growth within the United States, global populations should not be forgotten and efforts should be directed to bring treatment to children in all areas.

While the collaborative model would bring significant improvements to healthcare, there are barriers towards such a system and the practical aspects of implementation may be difficult. One, a model of this sort would require a significant commitment of resources both financially and professionally. Creating consortia models would require physicians and researchers to move away from competitive cultural norms and the publish-or-perish phenomena. Policy changes would have to be made to incentivize collaboration and lower regulatory impediments. Some may argue that this may drain resources away from more pressing healthcare needs and that support should instead be funneled to research and development rather than a systemic model.

Electronic health records (EHRs) also pose a challenge to improving coordinated care between physicians and during research trials as there already numerous issues with sharing information caused by incompatible systems. A collaborative system needs a technological infrastructure that allows for sharing information but the current flaws in EHRs make this aspect a challenge. Problems which physicians have cited with EHRs include insufficient standards, concerns about privacy rules, difficulties matching laptops, and costs.[210] While a consortium system like the Children's Oncology Group offers a streamlined method to consolidate patient data among institutions, medical fields which lack such an entity would face more difficulties in sharing data. Sharing data also raises concerns about patient privacy. Personal patient information, including history and details of treatment, would be viewed by many more players

[209] Joffe, Steven, and Franklin G. Miller. "Ethics of cancer clinical trials in low-resource settings." *Journal of Clinical Oncology* 32.28 (2014): 3192-3196.
[210] Mitka, Mike. "Physicians Cite Problems with EHRs." *JAMA* 311.18 (2014): 1847-1847.

in a collaborative system including a greater number of researchers or institutions and healthcare providers that are not doctors such as nutritionists or physical therapists. Growth in collaborative models should be cognizant of issues in patient privacy and should expand in ways that ethically preserve the rights of patients.

Additionally, there are merits to a competitive system as it has fueled growth and innovation in numerous sectors of this country's economy. Simply put, it is an integral component of the American capitalist system. Many believe that competition is the ideal and most efficient method for innovation and discouraging it would have more negative impact than benefit. When one of the primary goals is to spur innovation, the question then becomes how to best balance competition and collaboration. When there are so many stakeholders involved, including pharmaceutical companies, academia, hospitals, disease advocacy groups, etc., and each is regulated by different entities, creating uniform change becomes bureaucratically difficult. When compounded with different strategies and goals in every group, moving towards a collaborative system has major hurdles. Regulatory issues, standardization of practice, and intellectual property concerns would all have to be carefully managed.

Despite these challenges, collaboration in care and research holds significant value. Medicine ought to be patient-centric and the collaborative model leads to better results because it creates a better patient experience and focuses on the patient holistically. While advances in treatments and acceleration of research are important goals, the ultimate goal of medicine is to heal the patient. Collaborations in research place the patient before financial reward and collaboration in treatment allows the patient to supersede physician competition and receive holistic care that addresses all aspects of their sickness. Managing only the disease itself is not and should not be the only goal – the patient's psychological well-being, family support, and

long-term health also need to be treated and the collaborative model is one of the most efficient and effective ways to do so. Quality of life is greatly improved through a collaborative treatment approach.

Given the current climate surrounding the state of research it is becoming increasingly important to perform it with greater efficiency. Biomedical, scientific, and medical research are facing seismic cuts under the current presidential administration. As of early April 2017, President Trump has proposed to cut biomedical research by 18% by reducing the National Institute of Health budget by $5.8 billion.[211] While it is still uncertain whether Congress will support such cuts in biomedical research,[212] these proposals are representative of a larger issue of misconceptions of research and desire to move resources away from research.

Cooperative research models can mitigate the negative consequences of reduced funding and lead to a more efficient use of limited resources. Overlap is reduced and mechanisms to share data, such as through patient registries and biobanks, are created to the benefit of all players. Conflict of interest issues would be diminished as players align goals and mission from the beginning of the process, thus allowing faster translation of research developments into the clinical setting. As more drugs are created using genomic information and molecular targeting, precompetitive collaboration leads to a faster marketing of new agents because the preliminary scientific knowledge that these advancements rest on is shared amongst developers. The need for innovation within research remains critical – while the costs of developing pharmaceutical agents are rising, the pharma success rate is decreasing.[213] The pharmaceutical industry as a whole

[211] Pear, Robert. "Plan to Cut Funding for Biomedical Research Hits Opposition in Congress." *New York Times,* April 3 2017, web.
[212] Reardon, Sara, et al. "US science agencies face deep cuts in Trump budget." *Nature* 543.7646 (2017): 471-472.
[213] Scannell, Jack W., et al. "Diagnosing the decline in pharmaceutical R&D efficiency." *Nature reviews Drug discovery* 11.3 (2012): 191-200.

could benefit from modifications in structure to expand its cooperative efforts in order to yield better return on its investments.

This project has many avenues for growth and development. Interviewing pediatric oncologists may provide further insight into how collaborative practices are ingrained into the everyday lives of a practicing physician. Further understanding the specific dynamics and characteristics would provide more informed recommendations on translating this model to other medical fields. Scientific research is beginning to enter new fields, driven by advancements and technology and a greater understanding of the genome, especially with a growth towards personalized medicine. It is still unknown how these advancements will shape the nature of research in the future but identifying key niches for implementing collaboration could accelerate growth further. Further research can be performed on what types of policy changes may be need to be made to accommodate for application of this model. Specific areas of interest include health insurance policies, governmental guidelines for drug development, and intellectual property laws.

Finally, this project has explored what conditions may make a disease or medical field more conducive to the application of the collaborative pediatric oncological model. Identifying a few specific diseases with the most potential for benefit would allow for a more concrete expansion in cooperative care. . Performing economic and financial analyses on the potential costs to apply this model to fields outside of pediatric oncology would provide a better understanding on what aspects of the model should be applied and to what fields. Cost-benefit analyses would help inform a more efficient application of the model and would reduce wasted resources and time.

8 Conclusion

The purpose of this paper was to approach the field of pediatric oncology not from a medical or scientific perspective but from the viewpoint of innovation. Especially after overcoming a huge lack of scientific mechanisms that underlay childhood cancers to ultimately lead to extremely high treatment outcomes, it becomes apparent that this field of medicine has very unique characteristics that have led to its high success rate. By pinpointing these specific traits and understand what attributes and conditions allowed for the rise of such a successful model, the core transformative characteristics of pediatric oncology can be applied to other fields. Encouraging innovation is no easy task, especially when there are a multitude of stakeholders involved in the process yet pediatric oncology has managed to transform this impediment into a driving force for positive outcomes. The growth demonstrated in this field can be attributed to its collaborative practices, both in treatment and research, and it is this high level of cooperation that can ultimately transform other areas of medicine.

The success of pediatric oncology is an achievement that should be lauded, not only for the incredible growth and development it has seen over the last few decades but for its ability to unify players from all disciplines and even countries to address a single, important cause. The incorporation of collaboration has been fueled by necessity; the importance of these patients has motivated governmental agencies, institutions, and society to allocate a very large amount of resources to a small subsection of the population. This model has incredible potential to address a variety of other health issues facing the world today; collaborative efforts of this sort could be very effective in not only treating adult oncology but also a wide range of other diseases.

As technologies continue to progress and the scientific understanding of cancer becomes increasingly complex, it is important to continue addressing the issues that pediatric oncology

still faces. While many cancers have high success rates, most neurological and central nervous system cancers have a very low probability of survival. In order to address these cases as well as the decline in growth over the last decade, the introduction of new methods and policies is vital in sustaining progress. The model of pediatric oncology in the United States has managed to become a paradigm for successful research and treatment, and its incorporation of collaboration is a standard that should be applied to other industries to foster innovation.

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Biography

Arushi Pandya was born and raised in Austin and is a student of the University of Texas at Austin in the Plan II Honors Program and Biology. During her time at UT, she has been involved with Texas Orange Jackets, Student Government, the Plan II Premedical Society, stroke research in the Schallert Lab and developed interests in health policy and bioethics. Upon graduation, she will attend Dell Medical School and work towards creating a more innovative and equitable healthcare system.